VOLUME 59 NUMBER 5

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CLINICAL USE OF ANTIRETICULAR CYTOTOXIC SERUM IN DERMATOLOGY

Preliminary Report

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JAMAICA, N. Y.

IN THE past few years the Russian literature has included numerous papers dealing with the antireticular cytotoxic serum of Bogomelets. The *American Review of Soviet Medicine* introduced this subject to the American medical profession with translations of papers by Bogomelets, Marchuk, Linberg and Strazhesko.[1] Since then many investigators have instituted research and study of clinical problems to corroborate and check the results reported by the Russian investigators.

At a conference held in July 1942 at Ufa, Soviet Union, the action of antireticular cytotoxic serum was summarized as follows:

> Anti-Reticular Cytotoxic Serum, proposed by A. A. Bogomelets, is a powerful specific factor influencing the physiologic system of the connective tissue, exerting a strong stimulative action upon the cellular elements of the system if used in small doses, this having been established both by experimental investigations and clinical observations. Taking into account the fact that the physiologic system of the connective tissue has very important trophic and protective functions, the use of Anti-Reticular Cytotoxic Serum in therapeutic practice is to be recommended in all the various diseases which are connected with a weakening of inhibition of the functions of the system.

The antigen described by Bogomelets was made from fresh spleen and bone marrow of a human being dead not more than ten hours.

The antireticular cytotoxic serum used in this study was prepared by the injection of this human antigen intravenously into rabbits, according to the method described by Marchuk.[1] This was produced and supplied by Dr. Harry Goldblatt, Director of the Institute for Medical Research of The Cedars of Lebanon Hospital, Los Angeles. The doses used conformed to the schedule outlined by Dr. Goldblatt.

Dr. Fred Weidman interpreted many of the histologic sections.

Chief, Clinic of Dermatology, Graduate Hospital, Philadelphia, and Assistant Professor of Dermatology, Graduate School of Medicine, University of Pennsylvania (Dr. Samitz); formerly Resident in Dermatology, Philadelphia General Hospital (Dr. Stritzler).

1. Am. Rev. Soviet Med. **1**:101-127 (Dec.) 1943.

Although very little is mentioned regarding the action of serum in dermatologic conditions, it was felt that the efficacy of this serum could be more accurately evaluated if biopsy sections were examined before and after the administration of the serum in certain dermatoses, especially the lymphoblastomas, so that, if a stimulative action on the cellular elements did occur, it could be readily recorded in the examination of the histologic sections. The following is a preliminary report of the use of the serum for several dermatoses.

DESCRIPTION OF CASES

Twenty cases have been followed for periods ranging from three months to two and one-half years. The following dermatoses were treated:

1. Psoriasis in a white man aged 43—placque type, generalized, inveterate and of sixteen years' duration.

2. Exfoliative dermatitis in a Negro woman aged 52, cause unknown, of four months' duration.

3. Acrodermatitis chronica atrophicans in a white man aged 62, associated with ulcerations of the legs, of four years' duration.

4. Stasis ulcers: (*a*) in a white man aged 56, associated with dementia precox (in remission), of twelve years' duration; (*b*) in a white woman aged 65, with recurrent ulcer of twelve to fifteen years' duration, and (*c*) in a white man aged 65, of eight to ten years' duration.

5. Scleroderma: (*a*) in a white woman aged 35, generalized, moderate and of fifteen years' duration, and (*b*) in a white woman aged 62, whose legs were involved with ulceration of two years' duration.

6. Pemphigus: (*a*) in a white man aged 54 (vulgaris type), of one year's duration; (*b*) in a white man aged 50 (foliaceous type), of one year's duration; (*c*) in a white woman aged 48 (vulgaris type localized to the vulva), of one year's duration; (*d*) in a white man aged 58 (vulgaris type), of one year's duration, associated with arthritis deformans of thirty years' duration; (*e*) in a Negro woman aged 50 (vulgaris type), of two years' duration, and (*f*) in a white man aged 39 (foliaceous type), of two years' duration.

7. Lymphoblastomas:

Kaposi's idiopathic hemorrhagic sarcoma (*a*) in an Indian and Negro man aged 86, of many years' duration, and (*b*) in a white man aged 60, of many years' duration.

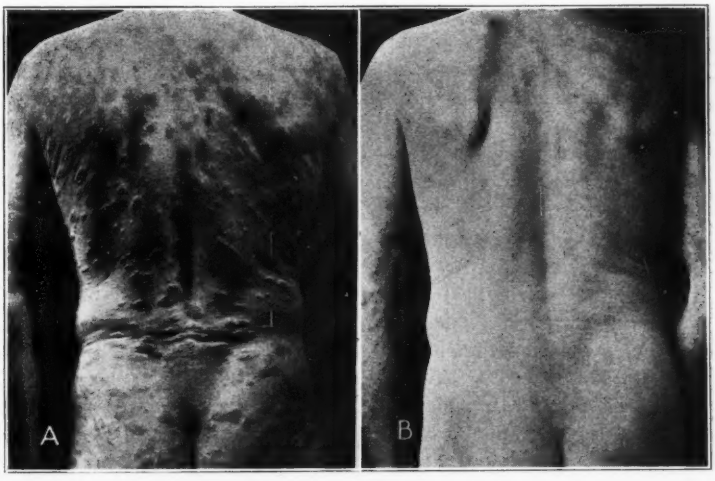
Mycosis fungoides (*a*) in a white man aged 52, of two years' duration; (*b*) in a white man aged 60, of seven years' duration, and (*c*) in a Negro aged 60, of one and a half years' duration.

Lymphosarcoma in a Negro aged 65, of four years' duration.

RESULTS

There were no subjective, objective or histologic changes noted when antireticular cytotoxic serum was used in 2 cases of scleroderma, 1 case of exfoliative dermatitis and 1 case of inveterate generalized

psoriasis. There were no subjective, objective or histologic changes observed in 4 cases (*a*), (*b*), (*d*) and (*f*) of the pemphigus group. In 1 case (*e*) there was a temporary improvement two weeks after the course of serum. This improvement lasted approximately four weeks. The remission was characterized by a feeling of well-being and increased strength and objectively by a considerable diminution of bullae on the trunk and in the mouth. Despite a maintenance course of ten weeks, a relapse occurred four weeks after treatment. In 1 case (*c*) there was no change in the vulvar lesions objectively or histologically; however, the patient volunteered that her general well-being was improved.



Mycosis fungoides in a white man aged 52 (case *a*): *A*, before treatment with antireticular cytotoxic serum; *B*, after treatment.

The 3 patients with stasis ulcerations and the 1 patient with acrodermatitis chronica atrophicans with ulcerations showed considerable improvement and healing of the chronic ulcers. These patients had previously been treated for many years with every known modality without much benefit. In 1 case (*a*) the ulcer was 75 per cent improved within two weeks after the last injection. This improvement had persisted when the patient was last seen, approximately eight weeks after the completion of the course of antireticular cytotoxic serum. There was no further improvement at the time. In the second case (*b*), one month after the last injection, the ulcer was almost completely healed. When the patient was seen six weeks later, improvement had been maintained. In the third case (*c*), definite

improvement (50 per cent) was observed three weeks after the course of treatment. However, six weeks later, there was a relapse.

In the patient with acrodermatitis chronica atrophicans 50 per cent improvement was noted within one week after the course of treatment with antireticular cytotoxic serum. Relapse, however, occurred ten weeks later, despite a maintenance dosage.

In 1 case of Kaposi's idiopathic hemorrhagic sarcoma there was a decided improvement in the general well-being of the patient after one course of treatment with the serum. No change, however, was seen in the lesions proper. No change was demonstrated in the histologic sections taken before and after treatment. Following the second course of treatment with the serum a year later, there was a decided lessening of the edema of the affected parts. There was no change in the histologic picture. In the second case of Kaposi's idiopathic hemorrhagic sarcoma there had previously been a therapeutic failure with roentgen rays and nitrogen mustard. Three weeks after the administration of the serum this patient stated that she experienced a feeling of well-being. This subjective improvement was still present after three months. Objectively, the bullous-like lesions appeared flatter and somewhat smaller. There was no change in the placque-like lesions. There was no change in the histologic sections.

In 3 cases of the mycosis fungoides group, histologic examinations of cutaneous sections taken before and after treatment showed no demonstrable change. One patient (*b*) who received one course of treatment with the serum had a short period of feeling well but then experienced a relapse. This patient showed no objective change in the cutaneous lesions. This patient had not the slightest relief from any previous medication, which included arsenic compounds, roentgen rays, chaulmoogra oil and nitrogen mustard. One patient (*a*) received several courses of the serum and then was maintained on small doses over a period of weeks. There was prompt improvement in the appearance of the lesions and a resultant feeling of well-being. This beneficial effect lasted three weeks after the first course and three weeks after the second course. When small doses were given every four days, a beneficial effect lasted two months. Previous treatment with arsenic preparations and roentgen rays was without benefit. One patient (*c*) received antireticular cytotoxic serum after a relapse following nitrogen mustard and previous roentgen ray therapy. Temporary improvement of the skin lasted two months. The more significant feature was the decided improvement in the patient's appetite and general well-being. In 1 case of the lymphoblastoma group (the case of lymphosarcoma) two courses of antireticular cytotoxic serum were administered. Each course resulted in a prompt disappearance of

the lesions. The beneficial effect of the first course lasted eight months. The beneficial effect of the second course lasted two months. After treatment decided changes in successive histologic sections were noted. This patient previously was treated with roentgen rays without benefit.

CONCLUSIONS

Antireticular cytotoxic serum was of no value in 2 cases of scleroderma, 1 case of exfoliative dermatitis, 1 case of generalized psoriasis and 6 cases of pemphigus. Results to date indicate that antireticular cytotoxic serum proved beneficial in 4 cases of chronic ulcerations of the legs. The serum may produce temporary remissions in some cases of lymphoblastoma after the disease has failed to respond to treatment with other remedies. The results, however, were not consistent and did not permit a definite interpretation. Further investigation will prove or disprove the efficacy of this serum as an adjunct to treatment in these conditions.

FACTORS IN AMORPHOUS PENICILLIN G INFLUENCING GROWTH OF FUNGI

I. Effect on Elaboration of Trichophytin by Trichophyton Gypseum

SAMUEL M. PECK, M.D.
AND
K. K. LI, M.D.
With the Assistance of Rose Bergamini, B.A.
NEW YORK

THERE are a number of in vitro methods for evaluating the fungicidal and fungistatic activity of therapeutic agents.[1] However, the clinician is often confronted with discrepancies between the laboratory data and the clinical effectiveness. This situation is due in part to the fact that in the testing of fungicides in vitro there is not considered the special circumstance which is present in most fungous

From the Dermatologic Service of Mount Sinai Hospital.

This work was supported by a grant from the Lederle Laboratories.

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

1. Peck, S. M., and Rosenfeld, H.: The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, J. Invest. Dermat. **1**:4, 1938. Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Rôle of Sweat as a Fungicide, with Special Reference to Use of Constituents of Sweat in Therapy of Fungous Infections, Arch. Dermat. & Syph. **39**:126 (Jan.) 1939. Burlingame, E. M., and Reddish, G.: Laboratory Methods for Testing Fungicides Used in the Treatment of Epidermophytosis, J. Lab. & Clin. Med. **24**:765, 1939. Criteria for Evaluation of Skin Disinfectants, report of the Council on Pharmacy and Chemistry, J. A. M. A. **121**:593 (Feb. 20) 1943. Emmons, C. W.: Examination of Germicides and Antibacterial Agents, Am. J. Pub. Health **35**:839, 1945. Rose, S. B., and Miller, R. E.: Studies with the Agar Cup-Plate Method, J. Bact. **38**:525, 1939. Ruehle, G. L. A., and Brewer, C. M.: United States Food and Drug Administration Method of Testing Antiseptics and Disinfectants, Circular no. 198, United States Department of Agriculture. Sharlit, H., and Muskatblit, E.: A Search for a New Method for the Determination of the Fungicidal Action of Chemicals, Arch. Dermat. & Syph. **25**:615 (April) 1932. The War and Dermatophytosis, with Special Reference to Treatment and Fungicide Testing, report of the Council on Pharmacy and Chemistry, J. A. M. A. **128**:805 (July 14) 1945. Foley, E. J.; Herrmann, F., and Lee, S. W.: The Effects of p_H on the Antifungal Activity of Fatty Acids and Other Agents, J. Invest. Dermat. **8**:1, 1947. Weidman, F. D.: The Laboratory Aspects of Epidermophytosis, Arch. Dermat. & Syph. **15**:415 (April) 1927. Hillegas, A. B., and Camp, E.: The Testing of Fungicides Insoluble in Water, J. Invest. Dermat. **6**:217, 1945. Kligman, A. M., and Rosensweig, W.: A Simple Quantitative Method for the Laboratory Assay of Fungicides, ibid. **10**:51, 1948.

diseases. This specific condition is due to the allergy to the fungus, which is the chief component in the clinical manifestations. It certainly exists in dermatophytosis of the feet, the fungous disease most commonly treated.

In our laboratory we have developed a method for the evaluation of fungicides which takes into consideration not only the fungicidal activity of a therapeutic agent but also the effect of the agent on the metabolism of the organisms. The metabolites with which we were chiefly concerned were those which we believe play a role in the phenomena of sensitization. The complete details of the method, as well as the evaluation by this means of a number of the popular fungicides, will be given in another publication. It was during the course of work with this method that the rather interesting and unexpected observations which we report were noted.

MATERIALS AND METHODS

In a previous communication,[2] it was shown that Trichophyton gypseum was capable of producing a more alkaline p_H in Sabouraud's bouillon when grown on a medium with an initial p_H of 4.0 to 8.0. When the initial p_H was from 9.0 to 10.0, the organism acidified the medium. It was also demonstrated that there was a relationship between the changes in the hydrogen ion concentration in Sabouraud's bouillon and the appearance and concentration of the skin test factor (trichophytin). When the culture medium was initiated at a p_H on the acid side and the p_H rose only slightly, there was an increase in the skin test factor. The concentration of this factor roughly paralleled the rise in the hydrogen ion concentration. When the mediums were initially on the alkaline side, especially when phosphate buffers were used to bring the p_H up to 9 or 10, and there was a change in the p_H toward the acid side during growth, the skin test factor was formed in minimal quantities or not at all, as long as the p_H kept dropping.

It has been shown that the bouillon as well as the pellicle contained the skin test factor.[3]

Sabouraud's bouillon, used in our experiments, was prepared by adding 40 Gm. of dextrose and 10 Gm. of neopeptone® (Difco) to 1 liter of distilled water. The solution was then placed in an Arnold sterilizer for ten minutes and finally filtered through Wattman's no. 4 filter paper while it was still hot. A solution of merthiolate® (1:10,000) was added as a preservative.

In the present experiments, Sabouraud's bouillon was inoculated with T. gypseum; the same strain of organism was used throughout the experiments. A ten day culture of T. gypseum on a slant was used. A few cubic centimeters of an isotonic solution of sodium chloride was added and the mixture shaken vigorously; 1 cc. of the resultant spore suspension was used for inoculation into

2. Peck, S. M.; Glick, A., and Weissbard, E.: Trichophytin: The Apparent Separation of the Skin-Reactive Factor from the Therapeutic Principle in Trichophytin, Arch. Dermat. & Syph. **44**:816 (Nov.) 1941.

3. Peck, S. M., and Glick, A.: Trichophytin: Methods of Preparation with Special Reference to the Specific Skin-Reactive Factor, Arch. Dermat. & Syph. **43**:839 (May) 1941.

each flask. One hundred cubic centimeters of Sabouraud's bouillon was used in each flask. There were a number of control flasks for each experiment.

Readings of the p_H were taken at frequent intervals by means of the Beckman p_H meter. The flasks used to grow the organisms were constructed with a side neck at the base. This feature allowed frequent milkings, with a minimum danger of contamination.

The fractions were tested for their trichophytin content by the usual intradermal trichophytin test. As a control, a solution (1:30) of trichophytin (Lederle) was used. In each series of tests 6 to 12 patients were used, so that negative as well as positive reactions were present in each series. In this way nonspecific reactions as well as specific reactions could be evaluated. The grading of the reaction was 1 to 4 plus, as has previously been reported.

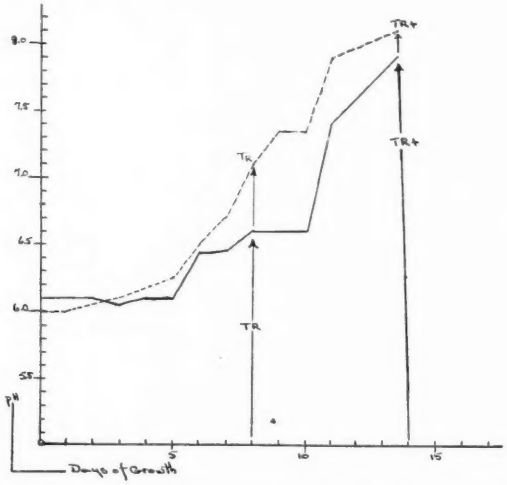


Fig. 1.—Changes in hydrogen ion concentration in Sabouraud's bouillon when 200,000 units of crystalline penicillin G is added to a culture of T. gypseum. In this figure and in figs. 2. 4, 5 and 6, *Tr* indicates a concentration of trichophytin equivalent to that in the control; *Tro*, no trichophytin demonstrated; *Tr+*, a concentration of trichophytin greater than that in the control, and *Tr—*, a concentration of trichophytin less than that in the control.

EXPERIMENTAL DATA AND RESULTS

EXPERIMENT 1.—The results observed are typical of the changes in the hydrogen ion concentration and formation of trichophytin when T. gypseum is inoculated in Sabouraud's bouillon at an initial p_H 6.0.

Results.—At the end of eight days there was usually a good subsurface growth, with the beginning of pellicle formation, and at the end of fourteen days the pellicle had spread appreciably over the surface in most flasks, with some variation from flask to flask.

Figures 1 and 4 show the gradual rise of the p_H. The formation of trichophytin roughly paralleled the increase in the p_H values. The

amount of trichophytin at the end of eight days compared favorably with that found in the solution of trichophytin (1:30). There was a moderate increase in the concentration of trichophytin at the end of fourteen days.

EXPERIMENT 2.—A series of experiments were made in which crystalline penicillin G was added to the Sabouraud bouillon in each flask before inoculation with the T. gypseum. In a typical experiment, the four flasks contained 100,000, 200,000, 300,000 and 1,000,000 units respectively of crystalline penicillin G.

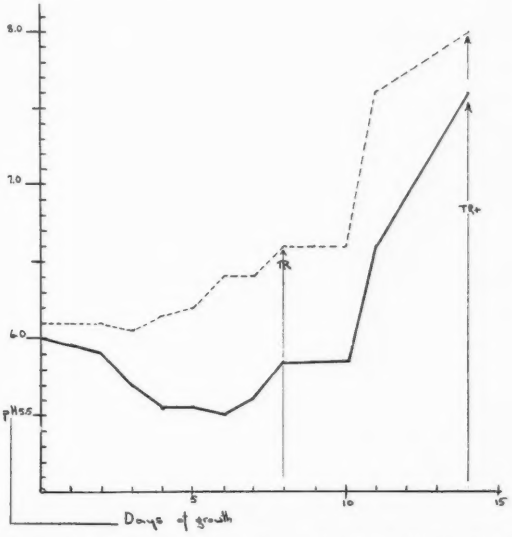


Fig. 2.—Changes in hydrogen ion concentration in Sabouraud's bouillon when 1,000,000 units of crystalline penicillin G is added to a culture of T. gypseum.

Readings of the p_H were made daily, and the cultures were milked at intervals of eight, fourteen and twenty days.

Results.—There was apparently no difference in growth in the flasks containing crystalline penicillin G as compared with the control, even when 1,000,000 units of crystalline penicillin G was added to a flask containing 100 cc. of Sabouraud's bouillon. This finding was common with the crystalline penicillin from various manufacturers. At the end of fourteen days, when there had been an appreciable rise in the p_H, the concentration of trichophytin in the flasks containing crystalline penicillin G was the same as that in the control flask.

It can, therefore, be concluded that even 1,000,000 units of crystalline penicillin G added to 100 cc. of Sabouraud's bouillon apparently

did not affect either the growth of the fungus or the formation of trichophytin (figs. 1 and 2).

EXPERIMENT 3.—For the experiments with amorphous penicillin G, materials available commercially, namely, the amorphous penicillin G manufactured by the Wyeth, Bristol, Eli Lilly and Lederle laboratories, were pooled. The total consisted of 16 vials, containing 2,800,000 units of amorphous penicillin G.

Growth Characteristics.—When 100,000 units of this amorphous penicillin was added to 100 cc. of Sabouraud's bouillon, there was definite

Fig. 3.—A 42 day culture of T. gypseum in Sabouraud's bouillon, with and without addition of 1,000,000 units of amorphous penicillin G.

retardation of growth, so that subsurface growth began later in the experimental flasks than in the control, and at the end of thirty-five days the surface pellicle in the flasks containing amorphous penicillin was approximately one-half the size of that in the control. The pellicle in the control flask covered three fourths of the surface at the end of thirty-five days. When 300,000 units of amorphous penicillin G was added, the subsurface growth began on the fourteenth day, and on the thirty-fifth day there was still no surface growth and only moderate subsurface growth. When 1,000,000 units was added, on the thirty-fifth day there was a very slight subsurface growth, with no surface growth at all (fig. 3).

Figures 4, 5 and 6 show a number of curves indicating the changes in p_H. It is seen that in the flask containing 1,000,000 units of amorphous penicillin G there was a slight, fluctuating rise in the p_H through the thirty-five day period of observation. With the 300,000 units, the change in p_H was more apparent, and when 100,000 units was used the changes in hydrogen ion concentration roughly paralleled those observed in the control, although the p_H in the flasks containing

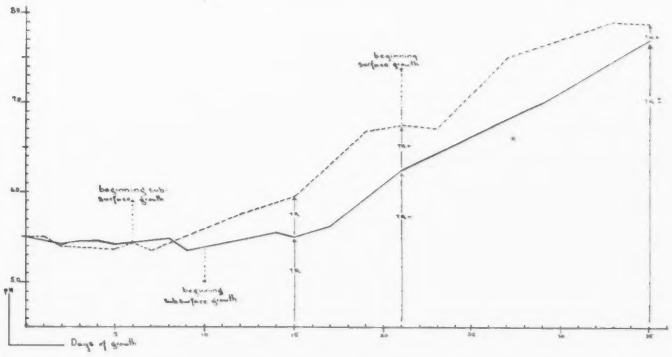


Fig. 4.—Changes in hydrogen ion concentration in Sabouraud's bouillon when 100,000 units of amorphous penicillin G is added to a culture of T. gypseum.

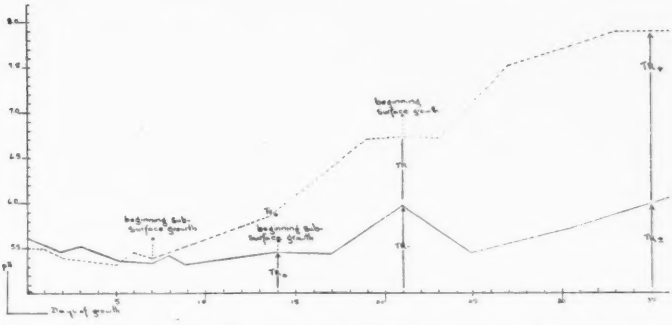


Fig. 5.—Changes in hydrogen ion concentration in Sabouraud's bouillon when 300,000 units of amorphous penicillin G is added to a culture of T. gypseum.

amorphous penicillin G did not rise as rapidly or as high in the thirty-five day period.

Formation of Trichophytin.—At the end of fourteen days, in the flask containing the 1,000,000 units of amorphous penicillin G, no trichophytin was formed, and neither was any formed at the end of thirty-five days (fig. 6). This result, of course, was to be expected

because of the practical absence of growth. With the 300,000 units, there was no trichophytin formed at the end of fourteen days; some was formed at the end of twenty-one days but definitely less than in the control, and at the end of thirty-five days the trychophytin had not increased in concentration (fig. 5). With the 100,000 units, at the end of fourteen days the trichophytin concentration was approximately the same as that in the control, and its increase paralleled the increase in the control during the subsequent period of observation (fig. 4).

COMMENT

Evidently there are factors in amorphous penicillin G which have a pronounced retarding effect on the growth of fungi. It is difficult, of course, judging from the experiments presented, for one to be sure just what the nature of these substances is. There is a possibility that this fungistatic material may be a chemical substance present in amorphous

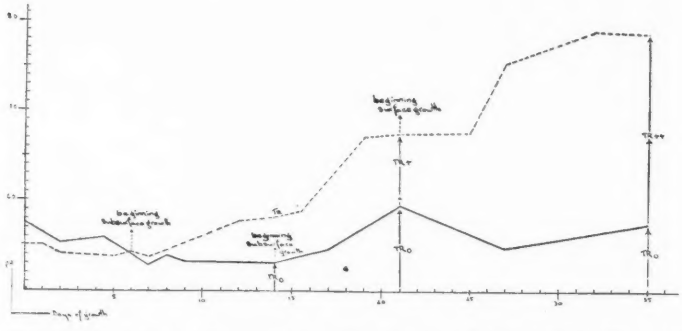


Fig. 6.—Changes in hydrogen ion concentration in Sabouraud's bouillon when 1,000,000 units of amorphous penicillin G is added to a culture of T. gypseum.

penicillin. That the factors are removed when penicillin is further refined is clearly indicated by their absence in the crystallized product. These experiments also indicate that amorphous penicillin G by itself has no effect on the growth of fungi, as was to be expected.

As pointed out previously,[2] and also as seen from experimental data reported here, there is a definite relation between changes in the hydrogen ion concentration and the elaboration of trichophytin by T. gypseum in Sabouraud's bouillon. The formation of the skin test principle roughly parallels the increase in the p_H values. The addition of crystalline penicillin G, even in amounts of 1,000,000 units to 100 cc. of Sabouraud's bouillon, modifies little the usual p_H curve accompanying the growth of the T. gypseum and, similarly, does not affect the formation of trichophytin.

The amorphous penicillin, on the other hand, definitely alters the p_H curve and also influences the formation of trichophytin. The amount of trichophytin formed is not directly related to the retardation of growth but roughly parallels here also the changes in the hydrogen ion concentration. The last observation is an important point, which will be discussed more fully in our article on the proposed method for evaluation of fungicides. We have been able to show that in some instances fungicidal substances, even when they definitely retard growth, allow an appreciable amount of trichophytin to be formed.

CONCLUSIONS

In certain lots of amorphous penicillin G there are apparently factors which suppress the growth of T. gypseum in Sabouraud's bouillon. The retardation in growth is reflected in the decreased formation of trichophytin in the bouillon.

Crystalline penicillin G has no retarding effect on the growth of T gypseum in Sabouraud's bouillon. It also does not influence the formation of trichophytin in the bouillon.

The fungistatic principles in amorphous penicillin G are not found in crystalline G as it is now commercially available. Their nature remains to be determined.

33 East Seventieth Street (21).

ABSTRACT OF DISCUSSION

Dr. George Lewis, New York: It is a pleasure to have the opportunity to open the discussion of this paper, which represents considerable experimental work.

At Cornell, our efforts were directed mainly toward an attempt to explain the well known phenomenon following the administration of penicillin, in which flare-up occurs in preexisting dermatoses and other fungous diseases. By means of observations on animal and human volunteers, it was shown that there is a definite connection between trichophytin elaborated by fungi causing the superficial fungous disease and the later administration of penicillin. It is well known that penicillin has many fractions, and Dr. Peck has also shown that trichophytin is not homogeneous material. I should like Dr. Peck to explain the apparent contradiction when he reports on the growth of T. gypseum. Clinically, one often sees just the opposite effect.

Dr. Samuel M. Peck, New York: I wish to thank Dr. Lewis for his fine discussion.

The factor which we have found may possibly play a role in sensitivity to penicillin. This factor also may be a contaminant which is not found in all lots of penicillin.

There is increasing awareness that in the refinement of penicillin many valuable factors are discarded which may be of clinical therapeutic significance.

CALCIFYING EPITHELIOMA OF MALHERBE

Report of Fifteen Cases, with Comments on Its Differentiation from Calcified Epidermal Cyst and on Its Histogenesis

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AND
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BOSTON

THE DIAGNOSIS of calcifying epithelioma of Malherbe is only rarely made on clinical grounds but is, as a rule, easily made by histologic examination. Only one other tumor, calcified epidermal cyst, resembles calcifying epithelioma in its microscopic appearance.

On the basis of 15 cases the clinical and histologic characteristics of calcifying epithelioma of Malherbe will be described. Its histologic differentiation from calcified epidermal cyst will be discussed. Furthermore, the histogenesis of calcifying epithelioma will be commented on. The theory that calcifying epithelioma develops from immature hair matrix cells is supported.

CLINICAL DATA

Incidence.—Calcifying epithelioma is not particularly rare. Ch'in [1] found 10 such tumors among 22,000 routine surgical specimens, while Highman and Ogden [2] found 11 tumors among 24,185 specimens.

At the pathology laboratory of the Massachusetts General Hospital 29,488 surgical specimens were received from Jan. 1, 1945 to Jan. 31, 1948. Fifteen were diagnosed as calcifying epithelioma of Malherbe. Thus the incidence of approximately 1 such tumor per 2,000 specimens noted by Ch'in and by Highman and Ogden is confirmed.

Age.—Calcifying epithelioma may occur at any age but most frequently arises in early adult life. In Ch'in's series,[1] in 14 patients, the tumor appeared before the age of 20; in 8, between the ages of 21 and 50, and in 9, after 50.

In our series 9 tumors arose in patients under 20 years of age; 4 tumors arose in patients 21 to 50 years of age, and 2 tumors arose

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1. Ch'in, K. Y.: Calcified Epithelioma of the Skin, Am. J. Path. **9**:497, 1933.

2. Highman, B., and Ogden, G. E.: Calcified Epithelioma, Arch. Path. **37**: 169 (March) 1944.

in patients over 50. The youngest patient was 9 months old, and the oldest, 60.

Sex.—Calcifying epithelioma occurs more commonly in female than in male patients. In Muehlon's review [3] 59 patients were female and 26 were male.

In our series 10 patients were female and 5 were male.

Location.—Calcifying epithelioma is found most frequently on the face and on the upper extremities but may occur elsewhere on the body. No instance, however, of occurrence on the palms or soles has been recorded. Ch'in, in reviewing 95 cases of the tumor, found 48 located on the head, 19 on the upper extremities, 15 on the trunk, 9 on the neck and 4 on the lower extremities.

In our series the tumors were distributed as follows: Five were located on the head, 7 on the upper extremities and 1 each on the trunk, the neck and the lower extremities.

Gross Appearance.—The tumors are hard to the touch. They are adherent to and freely movable with the skin. On section they are gritty. Several tumors described in the literature [2] required, because of pronounced calcification or ossification, decalcification before sectioning. They may vary from 0.5 to 5.0 cm. in diameter. Most tumors, however, measure 1 to 3 cm.

In our series, none of the tumors contained sufficient amounts of calcium to require decalcification before sectioning. All the tumors were small, ranging in diameter from 0.5 to 2.0 cm.

Recurrences and Malignant Degeneration.—Occasionally recurrences following excision have been reported in the literature.[4] Malignant degeneration, however, does not seem to occur. The only case in which it was reported was that of Gromiko.[5] It is doubtful whether this tumor represented an instance of calcifying epithelioma of Malherbe, because the tumor cells showed a tendency to undergo rapid, full necrosis rather than to change into shadow cells.

In our series no recurrences were observed after excision. The period of follow-up varied from two to thirty-six months.

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3. Muehlon, W. F.: Zur Kenntnis des Malherbe'schen Epithelioms, Schweiz. Ztschr. f. Path. u. Bakt. **5**:53, 1942.

4. Reverdin: Epithéliome calcifié, opéré et recidivé, Rev. de chir. **24**:532, 1901. Malherbe, A.: L'épithéliome calcifié, ibid. **32**:651, 1905. Frey, E. K.: Das Psammokarzinom der Haut mit besonderer Berücksichtigung seiner Verkalkung, Frankfurt. Ztschr. f. Path. **24**:497, 1920.

5. Gromiko, N.: Zur Kenntnis der bösartigen Umwandlung des verkalkten Hautepithelioms, Virchows Arch. f. path. Anat. **265**:103, 1927.

HISTOLOGIC DATA ON CALCIFYING EPITHELIOMA

Our 15 cases of calcifying epithelioma showed a histologic picture essentially the same as that described in recent communications by Ch'in,[1] Sutton and Sutton,[6] Côté,[7] Turhan and Krainer,[8] Muehlon,[3] Highman and Ogden[2] and King.[9]

All the 15 tumors in our series were, on histologic examination, seen to be circumscribed and showed no connections with the epidermis. A fibrous capsule surrounded the tumor either partially, as it did in 10 cases, or completely, as it did in 5 cases (table). Embedded in a connective tissue stroma, variously shaped masses of epithelial cells were present. In 12 cases these masses were composed of two types

Histologic Data on 15 Cases of Calcifying Epithelioma of Malherbe

Case No.	Duration of Tumor, Mo.	Basophilic Cells	Transition of Basophilic Cells Into Shadow Cells	Small, Round Centers of Keratinization	Sheets of Keratinization	Calcification	Melanin	Fibrous Capsule
1	6	(+)	—	+	+	++	+	Complete
2	4	(+)	—	++	+	++	—	Partial
3	30	—	—	(+)	++	+	—	Partial
4	4	+	+	++	++	—	—	Complete
5	12	(+)	—	+	++	+++	—	Partial
6	12	+	+	+	++	(+)	—	Partial
7	..	(+)	—	+	+	++	+	Partial
8	6	++	+	+	++	—	—	Partial
9	3	+++	+	+	+	—	—	Partial
10	1	(+)	+	+	++	++	—	Complete
11	3	—	—	+	++	—	—	Complete
12	..	—	—	+	++	+++	—	Partial
13	4	+++	+	+	++	+	—	Partial
14	5	++	+	+	++	++	—	Complete
15	2	+++	+	+	+	—	—	Partial

of epithelial cells, namely, viable basophilic and nonviable shadow cells (figs. 1 and 2). In 3 tumors, however (cases 3, 11 and 12), only shadow cells were seen.

Basophilic Cells.—The basophilic cells greatly resembled the cells of which the basal cell epithelioma is composed. They had large, round or elongated, deeply basophilic nuclei and only little cytoplasm, so

6. Sutton, R. L., and Sutton, R. L., Jr.: Calcifying Epithelioma, Arch. Dermat. & Syph. **31**:48 (Jan.) 1935.

7. Côté, F. H.: Benign Calcified Epithelioma of the Skin, J. Path. & Bact. **48**:575, 1936.

8. Turhan, B., and Krainer, L.: Bemerkungen über die sogenannten verkalkenden Epitheliome der Haut und ihre Genese, Dermatologica **85**:73, 1942.

9. King, L. S.: Mummified Epidermal Cysts (So-Called "Calcified Epitheliomas"), Am. J. Path. **23**:29, 1947.

that the nuclei were densely packed. In many areas the borders of the cells were indistinct, so that the nuclei appeared to be embedded in a symplasmic mass. In other areas the cells were separated from each other. Intercellular bridges, however, were nowhere seen. The number of basophilic cells varied but was in all 12 tumors smaller than that of the shadow cells. In 3 tumors (cases 9, 13 and 15) the number of the basophilic cells was between one fourth and one half that of the shadow cells; in 4 tumors (cases 4, 6, 8 and 14) it was approximately one tenth that of the shadow cells; in 3 tumors (cases

Fig. 1.—Calcifying epithelioma of Malherbe (case 13); hematoxylin-eosin stain, × 100. The epithelial masses of the tumor are composed of two types of cells, basophilic cells and shadow cells. The basophilic cells lie in bandlike arrangement around aggregates of shadow cells. The cell mass in the upper left corner contains in its center an area of calcification.

1, 2 and 10) only a few small groups of basophilic cells were present, and in 2 tumors (cases 5 and 7) some of the sections contained small groups of basophilic cells, while others contained none. The 3 tumors with the largest number of basophilic cells showed a moderate number of mitotic figures in the basophilic cells. The arrangement of the basophilic cells was of two types: The cells either were arrayed in bandlike fashion around masses of shadow cells (fig. 1) or lay in clusters of varying sizes and shapes (fig. 2). The bandlike arrange-

ment predominated in only 2 tumors, both of which contained a large number of basophilic cells. In the other 10 tumors arrangement in clusters predominated.

Shadow Cells.—The shadow cells stained pale pink with hematoxylin and eosin, while with eosin and methylene blue they stained from blue to purple. They had a distinct border but took no nuclear staining. Frequently they had a central, unstained "shadow" at the site of the nucleus. These nuclear shadows were more distinct with eosin-methylene blue stain than with hematoxylin-eosin stain. Although as a rule the change from basophilic cells to shadow cells was abrupt, there

Fig. 2.—Calcifying epithelioma of Malherbe (case 9); hematoxylin-eosin stain, × 100. The basophilic cells lie in irregular groups and not in bandlike arrangement, as they do in figure 1.

were in several tumors (cases 4, 6, 8, 9, 10, 13, 14 and 15) areas in which the gradual development of basophilic cells into shadow cells could be observed (fig. 3).

Calcification.—Calcification was present in 10 and absent in 5 tumors. Thus it was by no means an obligatory finding, as the name given to the tumor would imply. In some tumors calcification was present in only a few small areas (cases 3, 6 and 13), while in others it was extensive (cases 5 and 12). In general, an inverse relation seemed to exist between the number of basophilic cells and the degree

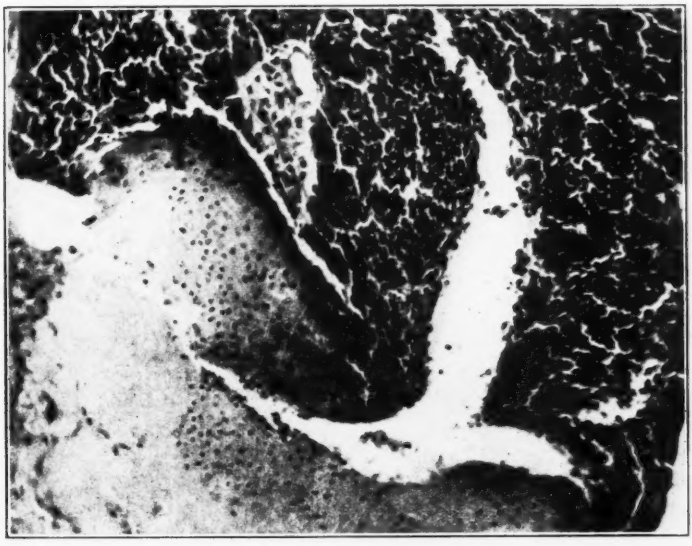

Fig. 3.—Calcifying epithelioma of Malherbe (case 9); hematoxylin-eosin stain, × 200. The gradual development of basophilic cells into shadow cells can be observed.

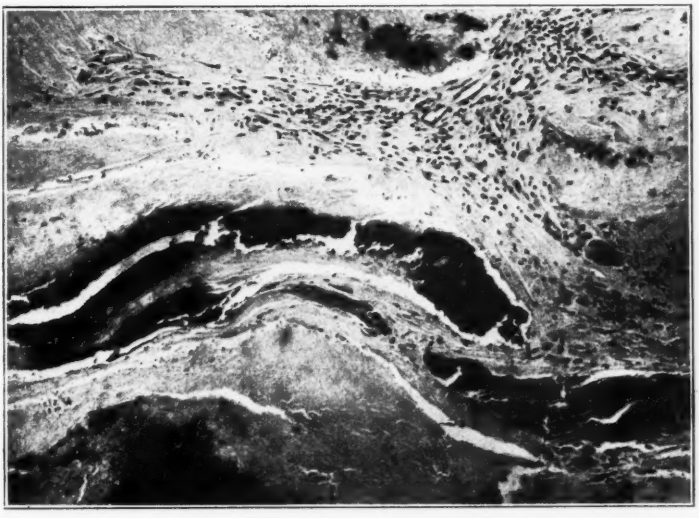

Fig. 4.—Calcifying epithelioma of Malherbe (case 7); hematoxylin-eosin stain, × 100. Large solid sheets of calcified material replace areas of shadow cells.

of calcification. Only 1 tumor (case 11) was an exception, in that it contained neither basophilic cells nor calcified material. The deposits of calcium were observed only in areas of shadow cells. They were never seen in basophilic cells, nor were they observed in the stroma. The calcium was present either as fine granules filling the shadow cells or as large solid sheets replacing areas of shadow cells (fig. 4).

Ossification.—Ossification, which is a relatively rare occurrence, was not seen in any of the 15 tumors in our series.

Cornification.—Areas of cornification were present in every one of the 15 tumors. However, the areas of cornification were usually

Fig. 5.—Calcifying epithelioma of Malherbe (case 2); eosin-methylene blue stain, × 100. Small, round centers of cornification are present in masses of shadow cells.

small. Several forms of cornification were observed. One could observe in some areas the evolution of sheets of shadow cells into sheets of horn cells. In addition, all tumors showed, some conspicuously, small, round centers of cornification within the masses of shadow cells (fig. 5). In 6 tumors (cases 6, 8, 9, 13, 14 and 15) similar centers of cornification were observed also in areas of basophilic cells (fig. 6). Cornification in the small, round centers tended to be abrupt and complete.

Melanin.—Melanin was observed in 2 of the 15 tumors. In the tumor of case 1 melanin was observed in large amounts in several areas

of shadow cells. Only small amounts were seen in the stroma. In the tumor of case 7 melanin was present in small amounts in several of the small islands of basophilic cells but abundantly in the stroma. In both tumors the melanin located in the stroma was present extracellularly, as well as within phagocytic cells.

Stroma.—The connective tissue stroma in which the epithelial masses were embedded was in most tumors rich in cells. In tumors with extensive calcification the stroma had in some areas a hyalinized appearance and possessed only a few cells. Foreign body giant cells were observed in the stroma of each of the 15 tumors. In some they were present in large numbers. They showed a tendency to arrangement alongside the fields of shadow cells.

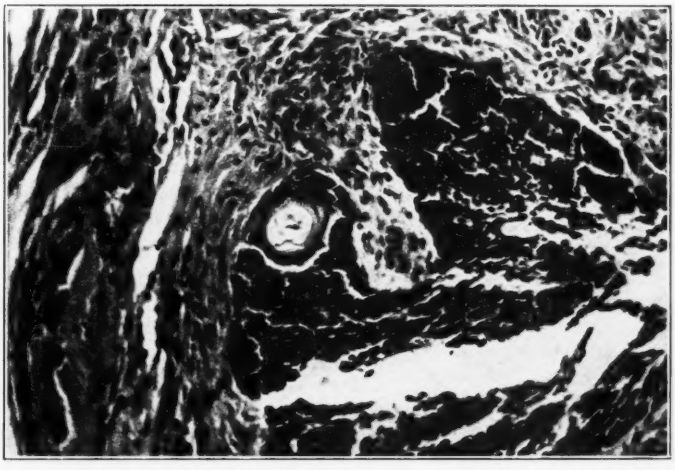

Fig. 6.—Calcifying epithelioma of Malherbe (case 9); hematoxylin-eosin stain, × 200. A small, round center of cornification is present in an area of basophilic cells.

HISTOLOGIC DATA ON CALCIFIED EPIDERMAL CYST AND DIFFERENTIAL DIAGNOSIS OF CALCIFYING EPITHELIOMA OF MALHERBE AND CALCIFIED EPIDERMAL CYST

A distinction between calcifying epithelioma of Malherbe and calcified epidermal cyst has not been made by all authors. Côté,[7] for instance, stated that calcifying epithelioma was "intermediate in type between epidermoid cyst and basal cell carcinoma." Fink,[10] however,

10. Fink, W.: Die verkalkenden Epitheliome der Haut und ihre Beziehungen zu Organisationsvorgängen in Atheromen, Virchows Arch. f. path. Anat. **289**: 527, 1933.

clearly outlined the distinctive features of the two types of tumors. Similarly, King [9] recognized a distinction between them, referring to one type as "mummified epidermal cyst" and to the other as "basal cell carcinoma with mummification."

Two cases of calcified epidermal cyst were observed. In the tumor of the first case the corium contained numerous masses of varying sizes, each composed of a layer of viable epithelium at its periphery,

Fig. 7.—Calcified epidermal cyst; hematoxylin-eosin stain, × 50. Variously shaped masses of epithelial cells are present. The masses are composed of a layer of squamous epithelium at their periphery, with keratinized material in their center. Several of the cell masses contain deposits of calcium.

with keratinized material in its center (fig. 7). Many of the masses, particularly the larger ones, contained extensive deposits of calcium within the keratinized material. The thickness of the peripheral layer varied; on the average, however, it was about the same as that of the surface epidermis. The composing cells were squamous cells which were eosinophilic and showed in some areas distinct intercellular

bridges. The change from squamous epithelium to keratinized material was usually abrupt, without the interposition of granular cells (fig. 8). The appearance of the keratinized material varied. In most areas there was full keratinization; in others the horn cells were parakeratotic, and in a few areas the borders of the cells were preserved and unstained shadows of the nuclei were recognizable. These cells were indistinguishable from the shadow cells seen in calcifying epithelioma of Malherbe.

The stroma in which the epithelial masses were embedded contained many cells, including a large number of foreign body giant cells.

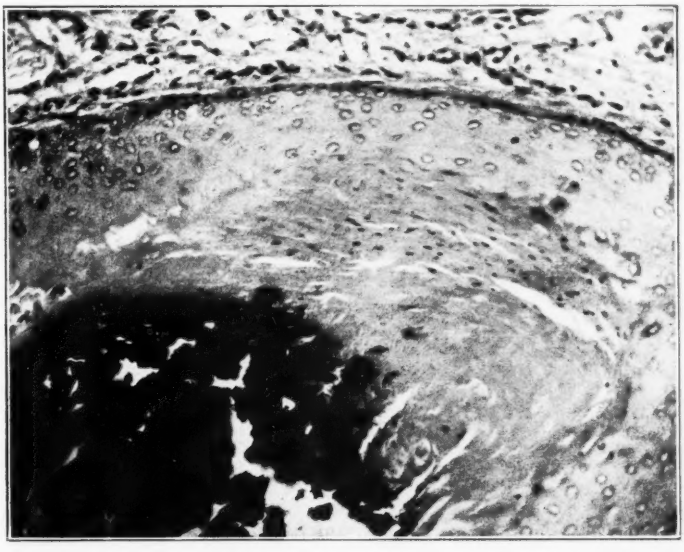

Fig. 8.—Calcified epidermal cyst; hematoxylin-eosin stain, high magnification of figure 7, × 200. The cells composing the peripheral layer are squamous cells with distinctly eosinophilic cytoplasm.

A few of the epithelial cell masses were not completely lined with squamous epithelium, and cellular granulation tissue had invaded them and replaced most of the horny material (fig. 7).

The tumor of the second case of calcified epidermal cyst was of the same type as that of the first case but differed from it by consisting of a single large mass, and not of numerous small masses. Only one third of the mass was lined with squamous epithelium. Elsewhere the epithelial lining was destroyed by invading granulation and fibrous tissue.

Calcifying epithelioma of Malherbe and calcified epidermal cyst thus have in common the presence of epithelial cell masses in which shadow cells (mummified cells) and keratinized material are present. Calcification occurs usually but not always within these cell masses. The cell masses are embedded in a stroma in which numerous foreign body giant cells are present.

The two types of tumor differ, however, in the following features: In calcifying epithelioma basophilic cells are present, and in calcified epidermal cyst, squamous cells. In calcifying epithelioma the basophilic cells tend to lie in irregular clusters, although occasionally they are arranged in bandlike fashion around masses of shadow cells. In calcified epidermal cyst the squamous cells always lie in bandlike fashion. In calcifying epithelioma shadow cells (mummified cells) are numerous and full keratinization is sparse, occurring mainly in small, round centers. On the other hand, in calcified epidermal cyst shadow cells are sparse and much fully keratinized material is present.

Thus the only absolute difference between the two types of tumors is the presence of basophilic cells in calcifying epithelioma of Malherbe and of squamous cells in calcified epidermal cyst. All other signs of differentiation are only relative. Difficulties in diagnosis arise in tumors, such as are occasionally observed, in which neither basophilic cells nor squamous cells can be found, but only shadow cells and keratinized material. It is probable that such tumors originally contained either basophilic or squamous cells, but that these viable cells gradually disappeared, either through evolution into shadow cells or horn cells or through destruction by invading granulation tissue. A decision as to whether such a tumor represents a calcifying epithelioma of Malherbe or a calcified epidermal cyst may be impossible.

King [9] had in his series of 9 cases 1 tumor with basophilic cells, which he called basal cell carcinoma with mummification; 2 tumors with squamous cells, which he called mummified epidermal cysts, and 6 tumors which contained only nonviable cells. He, somewhat arbitrarily, included these 6 tumors under the heading of mummified epidermal cyst. In our series of 17 tumors there were 12 which contained basophilic cells, 2 which contained squamous cells and 3 which contained neither. We have grouped, also somewhat arbitrarily, these 3 tumors under the classification of calcifying epithelioma of Malherbe because of the large number of shadow cells and the presence of keratinization in small, round centers. It may be the most satisfactory procedure not to force such tumors into either category, i. e., calcifying epithelioma of Malherbe or calcified epidermal cyst, but to put them into a separate group, which may be called shadow cell epithelioma or mummified epithelioma.

HISTOGENESIS OF CALCIFYING EPITHELIOMA

While the histogenesis of calcified epidermal cyst is obvious, that of calcifying epithelioma of Malherbe is not fully established. Originally described by Malherbe and Chenantais [11] as a calcified epithelioma of sebaceous glands, it has been variously regarded as a tumor of misplaced rests of sebaceous gland epithelium,[6] as basal cell epithelioma with degeneration instead of differentiation of cells,[12] or as a growth intermediate between epidermal cyst and basal cell epithelioma.[7]

Recently, Turhan and Krainer [8] expressed the opinion that calcifying epithelioma arises from hair matrix cells. They stated the belief that the basophilic cells are hair matrix cells and that the formation of shadow cells represents a form of keratinization, an attempt at hair shaft formation. In support of their theory, these authors pointed out that the basophilic cells resemble hair matrix cells, that the small, round centers of keratinization observed in the epithelial formations of these tumors resemble cross sections of hair shafts and that the melanin present in some of these tumors is analogous to the melanin found in normal hair. Highman and Ogden [2] arrived at similar conclusions.

Analysis of the tumors we have encountered tends to confirm the observations of Turhan and Krainer and of Highman and Ogden, namely, that the transformation of the basophilic cells into shadow cells represents a form of keratinization rather than of degeneration. The fact that further development of shadow cells into truly cornified cells could be observed in all the tumors we studied supports this theory.

The basophilic cells of calcifying epithelioma closely resemble the "basal cells" of basal cell epithelioma and of trichoepithelioma (epithelioma adenoides cysticum). Keratinization of the "basal cells" occurs in trichoepithelioma and in the keratotic type of basal cell epithelioma. It is probable that the keratinization in calcifying epithelioma of Malherbe is analogous to that in trichoepithelioma and keratotic basal cell epithelioma.

In a recent paper [13] the keratinization in trichoepithelioma and keratotic basal cell epithelioma was interpreted as an attempt at hair shaft formation. The "basal cells" in basal cell epithelioma and trichoepithelioma were regarded not as true basal cells of the epidermis but as primary epithelial germ cells. Since the primary epithelial germ,

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11. Malherbe, A., and Chenantais, J.: Note sur l'épithéliome calcifié des glandes sébacées, Bull. Soc. anat. de Paris **15**:169, 1880.

12. Muehlon.[8] Fink.[10]

13. Lever, W. F.: Pathogenesis of Benign Tumors of Cutaneous Appendages and of Basal Cell Epithelioma: I. Benign Tumors of Cutaneous Appendages, Arch. Dermat. & Syph. **57**:679 (April) 1948; II. Basal Cell Epithelioma, ibid. **57**:709 (April) 1948.

an embryonal structure, has the potentiality of differentiation into hair, sebaceous glands and apocrine glands, tumors originating from it may contain keratotic structures when differentiation is in the direction of hair.

We regard the basophilic cells in calcifying epithelioma as primary epithelial germ cells with a tendency to differentiation into keratotic hair cells. They thus have a function akin to that of hair matrix cells, but, being less mature than hair matrix cells, they produce not hair but irregular masses of immature hair cells (shadow cells). In a classification of primary epithelial germ tumors,[13] calcifying epithelioma of Malherbe may be placed under the heading of those with differentiation toward hair structures. Being circumscribed in growth, it must be regarded as more mature than keratotic basal cell epithelioma and as differentiated to approximately the same degree as is trichoepithelioma.

SUMMARY

Calcifying epithelioma of Malherbe is a benign cutaneous tumor having cell masses composed of two types of cells, namely, viable basophilic cells and nonviable shadow cells (mummified cells). The latter represent incompletely keratinized cells. The basophilic cells either are arranged in bandlike fashion around masses of shadow cells or lie in irregularly distributed clusters. The shadow cells develop from the basophilic cells. Calcification is often present but may be absent.

Calcifying epithelioma must be differentiated from calcified epidermal cyst. The latter differs from the former by the absence of basophilic cells and the presence of squamous cells which line the cell masses of the tumor either partially or completely.

Calcifying epithelioma of Malherbe is regarded by us as a tumor derived from the primary epithelial germ. We regard the basophilic cells as primary epithelial germ cells which, in calcifying epithelioma, have a tendency to differentiate into keratotic hair cells. The basophilic cells thus have a function similar to hair matrix cells; being, however, less mature than hair matrix cells, they produce not hair but irregular masses of immature hair cells (shadow cells).

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PSEUDO-OPHIASIS AND SICKLE CELL ANEMIA

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SICKLE cell anemia, which may occur in persons with the sickle cell trait, is practically confined to Negroes. It has some importance, not only because of the lesions and threats to life it produces but also because of the number of clinical states, such as perforated gastric ulcer, tuberculosis, rheumatic fever and disease of nerves, with which it may be confused. The dermatologist thinks of sickle cell anemia principally because of the ulcers, appearing usually on the legs, that are sometimes associated with it.

Sickle cell anemia is a hereditary constitutional anomaly in which the red cells may assume unusual shapes when the hemoglobin is in the reduced state. They may be drawn out and become elongated to crescentic forms, or be oat-shaped or irregularly stellate. The degree of anemia varies, but it may be great. Many reticulocytes and polychromatophilic cells are present, and often many normoblasts. The red cells show decreased fragility, and there is usually leukocytosis, with an increased number of platelets.

Three cases of sickle cell anemia are reported because of a peculiar type of alopecia which the subjects showed.

REPORT OF CASES

CASE 1.—K. B. R., a Negro aged 16, sought treatment for a punched-out ulcer on the lower third of the lateral surface of the left leg. It had been present for nine months. General physical examination showed nothing remarkable except for alopecia, which had been present since the age of 11 years on both sides of the scalp and which extended toward the occiput. The affected areas reached from the hair line to a relatively horizontal line about 1 inch (2.5 cm.) above the helix of the ear. There was a rough symmetry to the involved parts on the two sides. The scalp was not apparently inflamed and was normal in texture and color. The alopecia was not complete, but a diffuse, thin crop of stunted hairs remained. Their color matched that of the hair on the normal-appearing areas. Equal amounts of traction were necessary to remove the hairs at the affected and the unaffected sites. The patient complained of no unusual sub-

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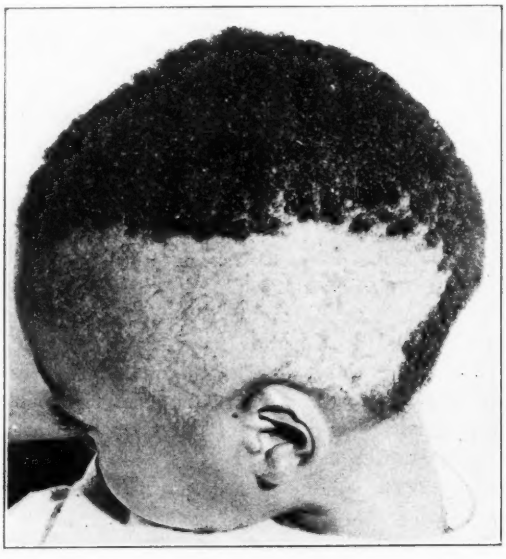
jective symptoms at the alopecic areas. Alopecia areata could be ruled out because of the diffuse, sparse hairs remaining, without patterning in circles or ovals. The parts involved had not changed their shape, nor was there shifting of areas. Examination of the hairs with a hand lens and a microscope did not show any differences between the pathologic and the normal parts. There were no nodosities or torsions, nor were the hairs frayed. There were no exclamation point hairs. The hairs from the affected sites were duller than those from the normal portion. No fungi were found either by direct examination or by culture.

The urine was normal, and a test of the blood serum for syphilis gave negative results. There were 2,100,000 red cells and 7,500 leukocytes, and the



Patient 3 (J. C.).

hemoglobin concentration was 40 per cent. The red cells displayed sickling. The icterus index was 14, and the sedimentation rate, 12.

Case 2.—L. L., a poorly developed Negro man aged 25, had been known to have sickle cell anemia for ten years (hospital record). He had had loss of hair about the margins of the scalp for seven years. The loss was intensified coincident with several crises of anemia. The preceding year a serologic test had shown him to have syphilis, for which he received treatment. He was in the hospital for the treatment of an anemic crisis. There was a zone of alopecia about 1¼ inches (3.2 cm.) wide, parallel to the hair margin and including it from the occiput to the temporal region. Its character was similar to that described in case 1. The urine was normal, and a serologic test of the blood for syphilis gave negative results. There were 2,600,000 red cells and 10,200 leukocytes,

and the amount of hemoglobin concentration was 45 per cent. Sickling of red cells could be shown. This patient was presented at a meeting of the Chicago Dermatological Society in 1947.

CASE 3.—J. C., a 5 year old Negro boy, entered the Children's Hospital with a temperature of 103 F., dry cough and anorexia.

Physical examination and roentgenologic study showed bilateral bronchopneumonia to be present. In addition, the spleen and liver were moderately enlarged, and mild icterus and marginal alopecia of the scalp were present. The parents stated that the child had been treated for symptoms of sickle cell anemia, but they did not remember how long the alopecia had been present. The loss of hair was somewhat symmetric on the two sides of the scalp. It extended from the frontal region backward to form a sort of rectangle. The middle third of the occiput and the scalp superior to it was spared. The alopecia was not complete, but the loss of hair was somewhat greater than that in the other 2 patients. Otherwise, its character was similar to that already described.

Laboratory Examination.—There were 1,500,000 red cells, with 58 nucleated forms per hundred white cells; active sickling; 30 per cent hemoglobin, and 25,000 white cells. Report of urinalysis showed nothing abnormal, and the serologic test for syphilis gave a negative reaction. The icterus index was 14.

COMMENT

All 3 patients were male, but their ages ranged from 5 to 25 years. All had severe sickle cell anemia. It appears that the alopecia, once formed, remains indefinitely. It does, however, vary in degree, the variation paralleling the changing severity of the subject's anemia. The alopecia could be thonght of as an inverse hippocratic one. It would have been desirable to make a histologic study of material from the scalp, but this material was not forthcoming. The alopecia is apparently not a family characteristic. How it is produced is pure conjecture.

SUMMARY

Three cases of a peculiar alopecia limited to the lateral parts of the scalp and associated with sickle cell anemia are reported.

30 North Michigan Avenue (2).

RELATIVE ALLERGENICITY OF STANDARD AND SUPPOSEDLY HYPOALLERGENIC NAIL POLISHES

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NEWARK, N. J.

THE FOLLOWING report is based on a study performed under a financial grant from an organization manufacturing nail polish for commercial distribution. The study was planned to elicit information valuable to the manufacturer, but, because it is believed that the findings will also be of interest to dermatologists, the report is here submitted identically as it was submitted to the sponsors, with their permission and with the addition of this introductory paragraph. The trade names of the four brands of commercial polishes used in the tests are withheld because they bear no relation to the findings or to the conclusions of this study.

During recent years a great deal of literature has appeared detailing the results of and drawing various conclusions from investigations on nail polishes. These studies have been made for both commercial and scientific reasons to determine the various causes of irritations and allergies resulting from the use of nail polishes. The conclusions have in many cases been corroborative of previous investigations, but divergent views have also occasionally resulted from similar studies. Thus it has become accepted that the various resins and plasticizers which are potentially allergenic are responsible for most of the difficulties encountered,[1] while the solvents are less important and the pigments of little consequence in causing trouble. Various commercial organizations have claimed that their products are hypoallergenic because, through periods of research, these manufacturers have developed new components which, they have stated, cause few allergic reactions. However, almost by definition a nail polish must consist of resin, plasticizer and solvent [1a] (with or without pigment), each with a specific purpose. While it may be that the resins or plasticizers used in hypoallergenic polish have a lower index of allergenicity than have other resins or plasticizers, nevertheless there almost has to be some degree of sensitivity to each resin or plasticizer

1. (*a*) Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1947. (*b*) Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940. (*c*) Schwartz, L., and Peck, S. M.: Cosmetics and Dermatitis, New York, Paul B. Hoeber, Inc., 1946.

as a specific substance, so that a person sensitive to one may not necessarily be sensitive to the others.

One of the claims recently made for a supposedly hypoallergenic nail polish was that of all the persons tested to it, none were allergic to the product in question who were not also allergic to other polishes and that, therefore, a person allergic to this polish which was claimed to be hypoallergenic might without further trial give up the idea of using any other polish. It would seem, however, that, since the polish is claimed to be hypoallergenic by virtue of a newly developed chemical component not present in other polishes, there should be some persons with sensitivities to this secret substance, who, in turn, have not had sensitivities to the components in the standard nail polishes and who would therefore be sensitive to the supposedly hypoallergenic product while they could use a standard one with impunity.

This hypothesis could be demonstrated only by indiscriminately taking persons for testing rather than by specifically selecting persons already known to be sensitive to another composition. With the method of using only selected cases already sensitive to another polish with a different composition one can obtain only one-sided and unscientific results, since every subject is selected because he is sensitive to one standard polish, and the tests performed on him will show only whether or not he is sensitive to the second polish as well. This same person might or might not be sensitive to the new substance to which he is tested, the likelihood being that, since it is a substance new to him, he would demonstrate no sensitivity to it, while he would continue to have the sensitivity which he showed originally to the standard substance.

If a series of tests with "unknowns" consisting of prepared nail polishes of various standard and supposedly hypoallergenic compositions were performed on an adequate number of persons who were unselected in relation to previous reaction to any other nail preparation, the statistics obtained might show whether a polish would be actually hypoallergenic per se or whether it would be so only for some one not as yet sensitized to its particular components. Also, such a series of tests might show whether or not a person who is sensitive to the components of one of the supposedly hypoallergenic polishes could use one of the standard makes.

I was given a series of specimens all unknown to me as to composition except for the fact that the red liquids were nail polishes of different composition and that the one clear solution was the resin used in one of these polishes, in the same percentage and in the same solvent as that actually used in the commercial product. The total number of specimens with which each subject was tested was six. Subsequent

to tabulating results of tests with each substance, I was informed of the identity of each specimen so that I might draw conclusions.

The series of six are designated according to the key number used when they were being tested, with the additional information given me at the end of the investigation:

Sample 1 was a standard, well known brand of nail polish.

Sample 2 was a standard, well known brand which had been claimed to have a lower allergenic index.

Samples 3 and 4 were well known, supposedly hypoallergenic polishes.

Sample 5, identical with sample 1, was placed in the series as a double check on the preciseness of the readings and was available for all the last 118 people tested.

Sample 5 A was the resin and solvent of sample 5, identically as used commercially, and was available for all the last 118 people tested.

Reactions of Ten Subjects to Tests with Various Nail Polishes and the Resin and Solvent

	Samples					
Subject No.	1	2	3	4	5	5A
3	..	..	±	..	..	..
7	+	..	+	..	..	..
30	+	±	..	±	..	..
50	±	++	..	+	..	..
59	..	++	+	±	..	..
132	..	±	..	..	..	..
162	±	+	..	..	±	±
165	..	..	±	..	..	..
202	..	..	+	±	..	..
225	..	..	..	++	..	..
Totals	4	5	5	5	1	1

Standard forms of patch tests were used, and, because of the number of tests applied, the scapular region was selected, the left for right-handed persons and the right for left-handed persons.

Previously, tests were made on other subjects in order that I might be certain that the products were not primary irritants. These tests were performed with the liquid polish on small portions of gauze, while the tests reported here, which are intended to demonstrate the allergenicity of the products, were performed with the polishes previously dried on pieces of gauze.[2]

A total of 233 consecutively appearing and unselected persons were tested with these substances. The ages varied from 2½ to 64 years, with the greatest number in the 20 to 45 year old group. There were almost equal numbers of male and female subjects.

2. Schwartz, Tulipan and Peck.[1a] Schwartz and Peck.[1c]

Of the total of 233 persons tested, 223 had no reactions to tests with any of the materials applied to the skin. The responses of the remaining 10 people to the materials tested are recorded in detail in the accompanying table.

SUMMARY

It will be noted from the table that of the 233 persons tested, only 10 were sensitive to any of the nail polishes and that no one reacted to all the four types used. Samples 2, 3 and 4 made an equally favorable showing with only five reactions, for a reactivity index of 2.15 per cent. Four people were sensitive to sample 1 in this series, which thus had a reactivity index of 1.72 per cent. No person had more than a mild reaction to samples 1 and 3, while samples 2 and 4 produced two and one more pronounced reactions, respectively.

In the last 118 tests, samples 5 and 5 A were used as a check on the preciseness of the readings. As was previously stated, sample 5 was identical with sample 1, and sample 5 A was its resin in the identical percentage and solvent used in samples 1 and 5. The identities of all samples used were withheld until all the results were tabulated, so that the observations and resultant conclusions could be made on a strictly objective basis. Samples 5 and 5 A reacted in all instances as did sample 1.

CONCLUSIONS

The conclusions that may be drawn from these statistics are as follows: Since people vary in their sensitivities to the organic chemicals involved, the same person may be sensitive to more than one of the chemicals, or he may be sensitive specifically to only one. When he is sensitive to one of the chemicals, a change to a brand of polish using a chemical to which he is not sensitive will allow him to use the latter polish without difficulty. The change may become necessary from a supposedly hypoallergenic polish to a standard make of polish; and, as indicated by this series, persons chosen at random are at least as sensitive to the components of the publicized hypoallergenic brands as they are to those of the standard ones.

The previously accepted beliefs that sensitivities to nail polishes are due essentially to the resins involved appear to hold true in this series of tests, although the purpose of this investigation was primarily to determine the comparative sensitivities of the several products tested. Also, it might be stated that, for combinations of such active components, nail polishes in general have a relatively low index of reactivity.

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VOGT-KOYANAGI SYNDROME

Report of a Case

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THE SYNDROME of uveitis with poliosis, vitiligo, alopecia and dysacousia, to which the name Vogt-Koyanagi syndrome has been given, has been recognized as a definite clinical entity for four decades. However, reference to it in dermatologic literature is sparse. It has been discussed mainly in ophthalmologic literature, probably because uveitis is the presenting and most disabling manifestation of the syndrome. But its dermatologic features are often striking enough, and of sufficient importance to warrant the attention and interest of dermatologists and the enlistment of their assistance in the investigation of the many mysteries attending this fascinating syndrome.

REVIEW OF THE LITERATURE

Although Schenkl (1873) and Jacobi (1874) had called attention to depigmentation of lashes in association with chronic uveitis [1] and although isolated associations of other features, such as Gilbert's (1910) of vitiligo and iridocyclitis, had occurred, it was Vogt [2] who, in 1906, first described the syndrome. Koyanagi [3] in 1929 described 6 cases, with a summary of the 16 cases reported by him and other writers up to that time. Carrasquillo [4] reported a case in 1942 and with it included an excellent review of the syndrome and a summary of findings in all 29

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Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Cal., April 27, 1948.

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2362.

2. Vogt, A.: Frühzeitiges Ergrauen der Zilien und Bemerkungen über den sogenannten plötzlichen Eintritt dieser Veränderung, Klin. Monatsbl. f. Augenh. **44**:228-242, 1906.

3. Koyanagi, Y.: Dysakusis, Alopecia und Poliosis bei schwerer Uveitis nicht traumatischen Ursprungs, Klin. Monatsbl. f. Augenh. **82**:194-211, 1929.

4. Carrasquillo, H. F.: Uveitis with Poliosis, Vitiligo, Alopecia, and Dysacousia (Vogt-Koyanagi Syndrome), Arch. Ophth. **28**:385-414 (Sept.) 1942.

cases, other than the 16 tabulated by Koyanagi, found in the world literature. Since that time there have been at least 8 other instances of Vogt-Koyanagi syndrome reported and several of a disease which may be etiologically related, Harada's disease (acute diffuse serous choroiditis with retinal detachment but with no involvement of the anterior segment of the eye, in which recovery is usual). The reports of Hague [5] and of Rosen [6] are particularly informative and complete in the more recent literature.

ETIOLOGIC CONSIDERATIONS

While the greatest number of cases have been reported from Japan, there is no limitation in geographic distribution. Adults in the third and fourth decades are apparently most commonly affected, with about equal distribution between the sexes. The cause of the syndrome is unknown. The similarity of the uveitis with that of sympathetic ophthalmia is well recognized. Peters [7] stated the belief that the destruction of the choroid pigment by the uveitis and dissemination of the products of this pigment led to a sensitization and allergic reaction in other pigmentary structures of the body (skin, hair and even the basilar membrane of the labyrinth). A virus has been suspected and its role investigated, without conclusive results, by a number of observers, including Hague,[5] Givner [8] and Laval.[9] The occasional prodromal transient encephalitis and influenza-like syndrome would lend support to this theory. There are also occasionally found mild changes in the cerebrospinal fluid (increased cells and pressure) early in the syndrome. Hague,[5] in his well documented discussion, carried this theory still further, postulated initial involvement of the hypothalamus and more specifically indicated a lesion of the fiber tract from the supraoptic portion of the hypothalamus to the hypophysis, affecting the pars intermedia and through it bringing about the various pigmentary disturbances. He attributed the uveitis to a severe inflammatory process secondary to the profound disturbance of pigmentary structures found in the uveal tract. Emotional disturbances and tumors of the hypothalamic region

5. Hague, E. B.: Uveitis; Dysacousia; Alopecia; Poliosis, and Vitiligo: A Theory as to Cause, Arch. Ophth. **31**:520-538 (June) 1944.

6. Rosen, E.: Uveitis, with Poliosis, Vitiligo, Alopecia and Dysacousia (Vogt-Koyanagi Syndrome), Arch. Ophth. **33**:281-292 (April) 1945.

7. Peters, A.: Sympathische Ophthalmie und Gehörstörungen, Klin. Monatsbl. f. Augenh. **50**:433-439, 1912; cited by Carrasquillo.[4]

8. Givner, I.: Bilateral Uveitis, Poliosis and Retinal Detachment with Recovery: Report of Case, Arch. Ophth. **30**:331-337 (Sept.) 1943.

9. Laval, J.: Bilateral Uveitis with Retinal Detachment, Poliosis, Alopecia, and Dysacousia, Am. J. Ophth. **29**:536-540, 1946.

have at times been suspected as causal. Harley and Wedding [10] reported isolation of actinomycetes from the aqueous and cerebrospinal fluids in their case, in which meningoencephalitis also was manifested.

CLINICAL FEATURES

A bilateral, widespread, chronic uveitis is the first feature of the syndrome to appear and may proceed rapidly to complete blindness and phthisis bulbi. Occasionally some vision is retained. Iritis and secondary glaucoma may be complications. According to Duke-Elder,[1] the changes in skin and hair appear from three weeks to three months after the ocular symptoms.

In order of frequency of occurrence,[4] the other symptoms are as follows:

1. Poliosis (82 per cent) of any hairy part, including the scalp, cilia and eyebrows. This may be temporary or permanent.

2. Vitiligo (62 per cent). A symmetric distribution and a tendency to migration are characteristic. This condition may resolve.

3. Alopecia (53 per cent). This is usually of the alopecia areata type. The hair may return.

4. Dysacousia (50 per cent). The symptoms may consist of hyperesthesia to noise, tinnitus and/or partial to complete deafness. This condition is usually bilateral and may appear shortly after the onset of the disease. It is transitory in many cases.

TREATMENT

Treatment is entirely symptomatic.[11] Atropine when indicated, sodium salicylate (6 to 8 Gm. per day) given empirically, potassium iodide and various types of nonspecific fever therapy have been used, along with a nourishing diet high in vitamins. Operative intervention is occasionally necessary.

REPORT OF CASE

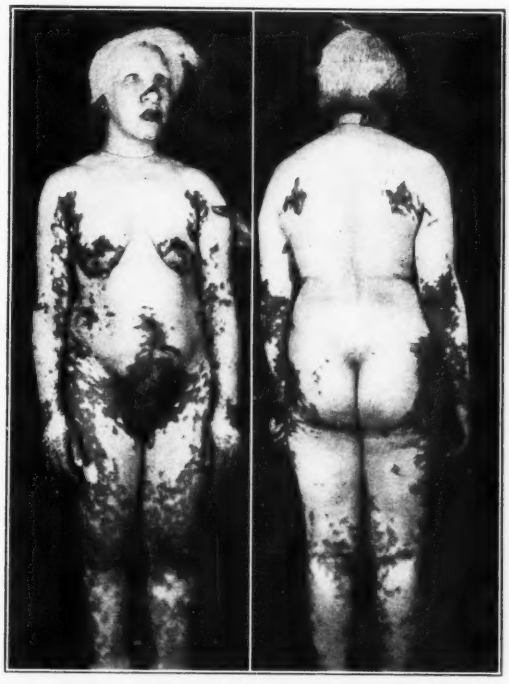
M. P., a 48 year old Negro woman, had had the left one of two congenital cataracts removed in 1927. Her vision was good until February 1946, when apparently glaucoma, with resulting blindness, developed in her left eye. Enucleation of this globe was performed because of associated severe pain. In May 1946 uveitis and pain became evident in the right eye, with subsequent complete blindness. About one week later hearing was lost in one ear, and a few days later, in the other ear. Since then the patient has been totally deaf. At about the same time, the hair, which had been jet black, started to become grayish white, and depigmented spots appeared, at first on the hands and face and later over widespread areas of the body. Some diffuse loss of hair has been noted, but there is no alopecia areata at the time of writing. The patient's speech is good, and she is apparently of average intelligence.

10. Harley, R. D., and Wedding, E. S.: Syndrome of Uveitis, Meningoencephalitis, Alopecia, Poliosis, and Dysacousia: Report of a Case Due to Actinomyces, Am. J. Ophth. **29**:524-535, 1946.

11. Carrasquillo.[4] Duke-Elder.[1]

Clinical Findings.—Examination showed enucleation of the left eye. The right eye was of low tension, with a hazy cornea and a pupil occluded by exudate, as seen with a slit lamp. No lens was seen, and the fundus was not visible. The iris was atrophic and irregular. There was no light perception. The hair at the scalp was gray-white and thick. Vitiligo, both confluent and patchy, was widely distributed (figure), so that most of the body was depigmented. Deafness was complete in both ears, but examination of the ears, nose and throat revealed no further abnormalities.

Pathologic Observations.—A specimen was removed for biopsy, including apparently normal skin and an area of depigmentation. Interpretation of the slide was made by Dr. Sachs as follows:



Vogt-Koyanagi syndrome in a Negro woman aged 48, bilaterally blind and deaf, with extensive vitiligo and poliosis.

"The epidermis showed no change except that in one half of the specimen there was no pigment in the basal cell margin, and, in the other half, pigment was uniformly distributed throughout the basal cells, as is normally seen in the skin of Negroes.

"The vascular changes were slight, and there was a sparse, diffuse infiltration of wandering connective tissue cells. There was an occasional chromatophore. Pronounced interstitial edema of the upper portion of the cutis was seen, and in this area there appeared to be moderate basophilic degeneration. The impression was that the condition was 'leukoderma.'"

Other laboratory studies and results were as follows: The Mazzini test gave a negative reaction. The urine was normal. The amount of blood urea nitrogen was 15 mg. per hundred cubic centimeters; of blood sugar, 95 mg.; serum protein, 8.3 mg. (with an albumin-globulin ratio of 5.6:2.7), and of serum cholesterol, 297 mg. Examination of the blood gave the following results: hemoglobin, 13.1 Gm. per hundred cubic centimeters; red blood cells, 4,600,000; white blood cells, 5,300, with 59 per cent lymphocytes, 6 per cent monocytes and 35 per cent polymorphonuclear leukocytes. Smear showed a few large young lymphocytes. A roentgenogram of the skull showed no abnormalities, and attempts at audiometric testing revealed a 100 per cent loss of hearing bilaterally.

SUMMARY

The Vogt-Koyanagi syndrome (uveitis, poliosis, vitiligo, dysacousia and alopecia) is briefly discussed and a case presented in which, at the time of writing, all the classic features of the syndrome except alopecia are manifested in a severe form.

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STURGE-WEBER SYNDROME

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PHAKOMATOSES [1] is the term that has been applied to the neurocutaneous syndromes. This term is derived from the Greek root φακός, which means "mother spot" or "mole" and implies a congenital factor. The three diseases which comprise this group and which have cutaneous lesions are (1) tuberous sclerosis, (2) neurofibromatosis of Von Recklinghausen and (3) Sturge-Weber disease. The first two are familiar to the dermatologist. However, there has been a paucity of dermatologic writing on the Sturge-Weber syndrome. In the American dermatologic literature cases have been reported by Goldberg,[2] who cited an instance of nevus flammeus (hemangioma congenitale) associated with glaucoma. Butterworth [3] reported the case of an epileptic idiot, a woman aged 20, with angiomatosis of the brain and a vascular nevus of the trigeminal area of the skin. Gammel [4] reported the case of a boy with a port wine nevus of the face associated with intracranial hemangioma with hemiplegia.

The Sturge-Weber syndrome consists of nevus flammeus in the distribution of one or all of the branches of the trigeminal nerve; convulsive seizures; hemiplegia, which is contralateral to the facial nevus; glaucoma; characteristic calcifications as evidenced by roentgenologic examination of the skull (appearing as sinuous, double-contoured lines, with the convolutions of the cortex on the affected side), and, finally, mental retardation.

From the Department of Dermatology, Northwestern University Medical School, Edward A. Oliver, M.D., chairman.

1. Brouwer, B.; van der Hoeve, J., and Maloney, W.: A Fourth Type of Phakomatosis, Sturge-Weber Syndrome, Kong. Acad. Wet. Verhandl. (Tweede Sect.) **36**:1, 1937.

2. Goldberg, S.: Nevus Flammeus with Glaucoma, Arch. Dermat. & Syph. **53**:503 (May) 1946.

3. Butterworth, T.: Angiomatosis of the Brain Associated with Vascular Nevus Involving the Trigeminal Area in an Epileptic Idiot, Arch. Dermat. & Syph. **35**:1159 (June) 1937.

4. Gammel, J. A.: Intracranial Hemangioma with Hemiplegia, Arch. Dermat. & Syph. **34**:698 (Oct.) 1936.

The following case, referred to me by Dr. Edward A. Oliver, presents the typical features of this syndrome with the exception of the pathologic ocular findings.

Past History.—J. G., a boy, was born on Sept. 26, 1943. The mother was in labor for forty-eight hours, and the child was delivered by cesarean section. He weighed 8½ pounds (3,855 Gm.) when born. A nevus flammeus was present at birth.

At the age of 10 months the child suddenly exhibited convulsive seizures associated with vomiting. The seizures, which were of a quivering sort, began in

Fig. 1.—Nevus flammeus covering the head, face and neck and the greater portion of the body.

the left hand and spread to the left arm and then to the left leg. Paralysis developed on the left side of the body, and it was not until Jan. 2, 1945, that the child was able to use his left arm and leg.

Physical Examination.—The greater portion of the right side of the face, including the right ear, was covered with a nevus flammeus which appeared more intense over the right side of the maxilla. The lesion was distributed over the regions of the ophthalmic and the maxillary branches of the trigeminal nerve. The left side of the face was involved in the area supplied by the mandibular branch of the trigeminal nerve. About 50 per cent of the surface of the left upper

extremity was involved. The right upper extremity and the right portion of the back and the chest were involved over much of their entire extent. The skin over the area supplied by the distribution of the nerves from the eleventh thoracic segment on the right side and over most of the right leg was involved (fig. 1).

The eyes were normal, with no evidence of glaucoma. The mucous membrane of the right side of the nasal septum was involved with nevus flammeus. In the mouth, the mucous membranes of the palate and upper gum showed angiomatous involvement.

The left upper extremity and the left lower extremity were smaller and weaker than the corresponding members on the right side.

Fig. 2.—Roentgenogram of the right side of the skull, showing wavy parallel lines of calcium deposits following the configuration of the vascular markings.

Laboratory Findings.—The urine contained no albumin or sugar. The red blood cell count was 4,210,000, with 11.6 Gm. of hemoglobin per hundred cubic centimeters, and the white blood cell count, 11,670.

Roentgenogram of the Skull.—There was intensive calcification involving the right side of the skull, where wavy parallel lines of calcium deposits followed a configuration of the vascular markings. The condition had the appearance of a calcified hemangioma. There were calcifications of the vessels, and vascular markings could be seen in the frontal, parietal and occipital lobes (fig. 2).

The sella turcica was within normal limits. There was considerable asymmetry of the head as seen in the anteroposterior projection, with the left side normal and the right side smaller than normal. The impression was of calcifications and hemangioma, with definite hemiatrophy of the skull on the right side. Roentgenograms of the chest revealed the lung fields essentially free from abnormality. The heart and the great vessels showed nothing unusual.

Roentgenologic examination of the pelvis and each femur revealed some tilting of the pelvis, with the right side higher than the left. The long diameter of the right femur measured 20.8 cm., while that of the left measured 20 cm. The right femur was somewhat larger than the left.

Treatment.—The patient received seven series of roentgen ray treatments (at St. Luke's Hospital), each treatment consisting of 600 r (measured in air), there thus being a total of 4,200 r in air given from Nov. 1, 1944, to Feb. 14, 1946; all were delivered to the right lateral aspect of the head. The physical factors used were 200 peak kilovolts and a Thoraeus filter with a half-value layer of 1.9 mm. of copper. Superficial grenz ray therapy was applied to the face and the hands.

When last seen by me, in April 1947, the patient showed improved use of the left arm and leg since the original visit.

HISTORICAL SURVEY

Schirmer [5] in 1860 first noted the coexistence of facial nevus with congenital glaucoma. However, he made no mention of epileptic convulsions or disease of the brain. It was Sturge [6] who in 1879 described the case of a 6½ year old girl with an extensive right-sided facial nevus, right-sided buphthalmos and epileptic convulsions beginning in the left hand. He expressed the conclusion that the right side of the brain was also involved in the nevoid condition. Kalischer [7] in 1897 published the first necropsy findings, confirming Sturge's contention that the brain was involved. Weber [8] in 1922 showed by means of roentgenograms that calcification of the brain was present on the same side as was the nevus. Full reviews were given by Greenwald and Koota [9] who in 1936 tabulated 82 records, and by Bergstrand and associates,[10] who in 1936 compiled data in 108 cases.

5. Schirmer, R.: Ein Fall von Telangiectasis, Arch. f. Ophth. **7**:119, 1860.

6. Sturge, W. A.: A Case of Partial Epilepsy, Apparently Due to a Lesion of One of the Vasomotor Centers of the Brain, Tr. Clin. Soc., London **12**:162, 1879.

7. Kalischer, S.: Demonstration des Gehirns eines Kindes mit Telangiectasis der linkseitigen Gesichtskopfhaut, Berl. klin. Wchnschr. **33**:1059, 1897.

8. Weber, F. P.: Right-Sided Hemi-hypotrophy Resulting from Right-Sided Congenital Spastic Hemiplegia, J. Neurol. & Psychopath. **3**:134, 1922.

9. Greenwald, H. M., and Koota, J.: Associated Facial and Intracranial Hemangiomas, Am. J. Dis. Child. **51**:868 (April) 1936.

10. Bergstrand, H.; Olivecrona, H., and Tönnis, W.: Sturge-Weber Krankheit, Gefässmissbildungen und Gefässgeschwülste des Gehirns, Leipzig, Georg Thieme, 1936.

TERMINOLOGY

Since Sturge's original report there have been many symptoms added to this syndrome. These nosologic differences have been due to the variability of the clinical and pathologic picture. Levy [11] and Green [12] suggested the designation of these conditions as encephalotrigeminal angiomatosis. In the past this syndrome was designated by the following names: Sturge-Weber disease by Bergstrand, Olivecrona and Tönnis,[10] Weber-Dimitri disease by Krabbe,[13] congenital neuroectoderm dysplasias by van Bogaert,[14] congenital ectodermoses (neurocutaneous syndrome) by Yakovlev and Guthrie,[15] Sturge-Kalischer disease by Weber,[16] Sturge's disease by Mussey and Miller,[17] Krabbe's disease by Moniz and Lima,[18] cutaneocerebral angioma by Charamis,[19] neurocutaneous syndrome by Kulchar and Anderson,[20] Brushfield-Wyatt syndrome by Brinton [21] and nevoid amentia.[22]

Of the above terms Sturge-Weber syndrome is in commonest usage, and thus this title is retained. Govaerts and Cambier [23] suggested the term vascular dysplasia. They deprecated the tendency to create new syndromes or to unite already well known ones under newly coined names. They expressed the opinion that the term phakoma, with its

11. Levy, G.: L'angiomatose du systeme nerveau central, Presse méd. **38**:37, 1930.

12. Green, J. R.: Encephalo-Trigeminal Angiomatosis, J. Neurol. & Exper. Neurol. **4**:27, 1945.

13. Krabbe, K. H.: Facial and Meningeal Angiomatosis Associated with Calcifications of the Brain Cortex, Arch. Neurol. & Psychiat. **32**:737 (Oct.) 1934.

14. van Bogaert, L.: Les dysplasies neuro-ectodermiques congénitales, Rev. neurol. **63**:353, 1935.

15. Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145 (Dec.) 1931.

16. Weber, F. P.: The Sturge-Kalischer Disease and the Sturge-Weber Panathenaic Amphora at Toronto, Brit. M. J. **1**:708, 1936.

17. Mussey, A. M., and Miller, H. H.: Sturge's Disease, Brit. M. J. **1**:822, 1939.

18. Moniz, E., and Lima, A.: Pseudo-angiomes calcifies du cerveau, angiome de la face et calcifications corticales du cerveau (maladie de Knud H. Krabbe), Rev. neurol. **63**:743, 1935.

19. Charamis, J. S.: Angiome cutanéocérébral, Rev. d'oto-neuro-opht. **12**:755, 1934.

20. Kulchar, G. V., and Anderson, L. E.: The Neurocutaneous Syndrome: The Congenital Ectodermoses, Arch. Dermat. & Syph. **30**:211 (Aug.) 1934.

21. Brinton, D.: Brushfield-Wyatt Syndrome, Proc. Roy. Soc. Med. **26**:846, 1933.

22. Cited by Mussey and Miller.[17]

23. Govaerts, P., and Cambier, P.: Angiomes caverneux multiples de la peau, des muqueuses, des os, et du système nerveux, Rev. belge sc. méd. **6**:419, 1934.

string of derivatives to include neurofibromatosis, tuberous sclerosis and the Hippel-Lindau syndrome, and the vague generalizations on which this nomenclature is based, is illogical and confusing.

ETIOLOGY AND PATHOGENESIS

According to Yakovlev and Guthrie [15] the Sturge-Weber syndrome, neurofibromatosis and tuberous sclerosis exhibit a remarkable parallelism in their clinical and pathologic manifestations; they are all the result of congenital maldevelopment bearing electively on the organs of ectodermal derivation: the nervous system, the eyeball, the retina and the skin. This theory is supported by the tendency of these lesions to metameric distribution in the skin and in the nervous system. The distribution of vascular nevi, however, seems to correspond with areas of sympathetic innervation rather than with true metameres, which observation suggests that such nevi may have their origin in some developmental defect of vasomotor innervation.

In the development of port wine nevi, mesodermal hyperplasia overshadows the ectodermal malformation, on the background of which the telangiectasia develops.

The three syndromes overlap one another in their clinical and pathologic manifestations; they have a common origin in a malformation of the ectoblast and clinically and pathologically can be included in one group under the term of congenital ectodermatoses. They differ in the period of disturbance of embryogenesis, in the predominance of one or the other ectodermal structures involved and in the degree of participation of mesodermal elements.

Luschka [24] was the first to point out that this type of vascular tumor of the brain usually results from a congenital abnormality of the embryonal capillary system. He stated that the hemangioma of the brain which is associated with cutaneous nevi arises from sequestration of a small portion of the embryonic capillary vascular system.

According to Verhoeff,[25] the development of vascular nevi takes place as follows: First, there is a destruction of, or an absence of, the function of the vasomotor nerves, which is followed by dilatation of the vessels. Next, the dilatation of the vessels produces a local increase in the tension of the capillaries, and then there is produced a compensatory hypertrophy, which, on account of the thinness of the walls, is manifested as a new growth of capillaries.

Von Barensprung [25] in 1863 was the first observer to advance the neurogenic theory of a nevus of the skin. He stated that (1) nevi

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24. Luschka, H.: Kavernose Blutgeschwulste des Gehirns, Virchows Arch. f. path. Anat. **6**:458, 1854.

25. Cited by Dunphy.[34]

usually appear on half of the body, not overlapping the midline; (2) they are manifested as streaks or spots on the skin which show an arrangement corresponding to the peripheral distribution of one or more spinal nerves, and (3) the degeneration of the skin depends essentially on a hypertrophy of the papillae of the skin, the same structures in which the peripheral nerves end. Von Barensprung stated the belief that a congenital disease of a single spinal ganglion originating in the uterus is the cause of the cutaneous degeneration which develops in the peripheral region of the corresponding nerve.

Weber [26] expressed the belief that this syndrome is not due to any genetic cause but to some "accidental" local injury (mechanical, chemical or physical) to the ovum at some period of fertilization, that is to say, to the embryo during the early intrauterine life.

There are a few observations which bear out the hereditary theory and suggest that a dominant factor may be operative. Oppenheim [27] in 1913 found that the mother of a 13 year old boy with a pial angioma, hemiplegia and jacksonian epilepsy had a cavernous angioma of the lip. Kufs [28] in 1928 gave details concerning a man aged 81 with an angioma of the face and brain and inferred from the previous history of one of the daughters that she had an angioma of the pons. Geyelin and Penfield [29] described calcification of the brain and epilepsy in a man and his four children. Cases have been reported in twins.[30]

Although practically all reported cases have been in white children, there has been a case reported in a Negro girl.[31]

CLINICAL FEATURES

Facial Nevus.—The type of cutaneous nevus seen with meningeal angioma is the port wine variety of hemangioma. It is a prominent sign and usually present at birth. It is usually dark purple but may be so inconspicuous as to escape notice, as in the case of Greenwald and Koota.[9]

26. Weber, F. P.: Rare Diseases and Some Debatable Subjects, London, Staples Press, Ltd., 1946, p. 9.

27. Oppenheim, H.: Ueber klinische eigentümlichkeiten kongenitaler Hirngeschwülste, Neurol. Centralbl. **32**:3, 1913.

28. Kufs, H.: Ueber heredo-familjäre Angiomatose des Gehirns und der Retina, ihre Beziegungen zu einander und zur Angiomatose der Haut, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651, 1928.

29. Geyelin, H. R., and Penfield, W.: Cerebral Calcification Epilepsy: Endarteritis Calcificans Cerebri, Arch. Neurol. & Psychiat. **21**:1020 (May) 1929.

30. Touraine, A.; Golé, L., and Sambron, J.: Epilepsie et angiomatose intracranienne chez deux jumeau, Bull. Soc. franç. de dermat. et syph. **43**:618, 1936.

31. Cohen, H. J., and Kay, M. N.: Associated Facial Hemangioma and Intracranial Lesion, Am. J. Dis. Child. **62**:606 (Sept.) 1941.

As a rule the cutaneous nevus is flat and composed of a superficial capillary plexus, but frequently the skin over it is raised and hypertrophied, or even rough and nodular, and in extreme instances the growth takes on the character of a sebaceous adenoma.[32]

The size of the nevus may vary from that of a minute pinhead to that of a growth covering the entire head, face and neck and the greater portion of the body, as in our case (fig. 1). The port wine nevus usually involves the face alone and there follows the distribution of one or more branches of the trigeminal nerve.

Cerebral Symptoms.—The cerebral symptoms, as mentioned by Mussey and Miller,[17] appear usually early in life, often before the end of the first decade. They correspond to the extent and position of the changes in the brain and usually consist in either jacksonian or generalized epileptic seizures, hemiplegia, hemiatrophy and a lesser or greater degree of amentia. The jacksonian fits, hemiplegia and hemiatrophy are, of course, on the side opposite to that of the facial nevus and the cerebral calcifications.

The angiomatous malformations of the brain are classified into three types.[33] They are (*a*) the telangiectases (chiefly capillary), (*b*) the venous angiomas and (*c*) the arterial or arteriovenous angiomas. When a facial nevus is present, the angioma of the brain is of venous origin. The venous angioma, unless it is associated with a facial nevus, is not likely to be diagnosed until it is unexpectedly exposed at operation or at autopsy. The venous angioma is rarely accompanied with a choked disk, in which respect it may differ from the arteriovenous angioma. The arterial angiomas, on the other hand, may often be recognized by an audible bruit, as well as by secondary effects, such as aneurysmal (arteriovenous) communications which lead to enlargement of the extracranial vessels, the carotid arteries or even the heart. Symptoms of arterial angioma appear later in life (in young adults), as compared with those of venous angiomas, which are present in infancy.

Ocular Symptoms.—Goldberg [2] stated that the glaucoma is associated with the facial nevus only if the nevus involves the eyelids or other ocular structures and that the causative factors in the production of the glaucoma are not always the same. The glaucomatous process is usually of the infantile type (buphthalmos), but it may be a simple chronic glaucoma developing later in life.

Dunphy,[34] in analyzing the causes of glaucoma, found that in 14 cases in which histologic examination was made, there were 10 angiomas

32. Greig, D. M.: A Case of Meningeal Nevus Associated with Adenoma Sebaceum, Edinburgh M. J. **28**:105, 1922.

33. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain, Springfield, Ill., Charles C Thomas, Publisher, 1928.

34. Dunphy, E. B.: Glaucoma Accompanying Nevus Flammeus, Am. J. Ophth. **18**:709, 1935.

of the choroid. In 1 case there were irregularities of Schlemm's canal and the scleral spur. In 1 case angiomatous changes in the iris extending to the iritic angle were present. In the remaining 2 cases no angioma or any obstruction of the iritic angle was found. Dunphy stated the conclusion, therefore, that in most cases the glaucoma can be ascribed to an obstructed filtration angle, due to angiomatous changes in the uvea, or to adhesions in the iritic angle resulting from the toxic action of degenerative changes within the eyeball.

Other ocular findings were mentioned by Moore [35] and include heterochromia iridis, coloboma of the disk, high refractive error and bilateral discoloration of the lens.

Roentgenologic Findings.—The roentgenologic appearance [17] of the skull is striking, especially in cases where extensive calcification of the brain has taken place. The calcified areas are confined to the affected half of the cerebrum, which is usually smaller than the sound companion. This observation may be inferred from a plain roentgenogram, in which the outline of the diseased half of the cerebrum can be clearly seen. The cerebellum is not involved. The shadows thrown by the calcium in the cortex are sinuous, and where the rays strike a sulcus at about a right angle two lines running 1 to 2 mm. apart can be seen. The commonest site of calcifcation is the occipital lobe.

Other Symptoms.—Some of the other symptoms occasionally present with this syndrome are mental retardation, tendency to adiposity, defects in memory, temper tantrums, errors in judgment, disturbance of speech, vertigo, headache, tremors and aphasia.

RELATION TO HYPERTROPHIC HEMANGIECTASIA

Weber [36] in 1907 called attention to a group of cases in which hypertrophy of one limb, or hemihypertrophy, depended, to some extent at least, on excessive vascularity of the affected parts, caused by the overgrowth of blood vessels. It seems that the hypertrophy affected not only the soft tissues, but also the bones. The abnormalities in question are congenital. The condition described is differentiated from Milroy's disease in that in the former there are (1) associated vascular abnormalities and (2) usually an increase in the length of the bones of the affected limb.

The association of hypertrophic hemangiectasia with Sturge-Weber syndrome is rare. Kalischer [7] presented the brain of a child aged 3½ months, in whom a right-sided hemihypertrophy was associated with a diffuse nevus flammeus, mainly of the hypertrophied side of the body.

35. Moore, R. F.: Hemangioma of Meninges Involving Visual Cortex, Brit. J. Ophth. **13**:252, 1929.

36. Weber, F. P.: Angioma-Formation in Connection with Hypertrophy of Limbs and Hemi-Hypertrophy, Brit. J. Dermat. **19**:231, 1907.

He mentioned that Arnheim and Heller in Berlin had shown similar examples of the association of diffuse cutaneous angioma with hemihypertrophy and that several similar cases were found to be described in the literature. Weber further mentioned that hemihypertrophy is not always associated with cutaneous angiomas and that the latter are not always limited to the hypertrophied side of the body. Cases of hypertrophic hemangiectasia have been reported by Senear,[37] Gray,[38] Pautrier and Ullmo [39] and Weidman.[40] Extensive reviews of hypertrophic hemangiectasia have recently been reported by Blumgart and Ernstene [41] and Gesell.[42]

In our case the left upper and lower limbs were smaller and notably shorter than the corresponding members on the right side; in fact, there was present a condition of right-sided hypertrophy such as one would expect to find in association with left-sided spastic hemiplegia.

PROGNOSIS

The immediate outlook for life is good.[17] In milder cases a useful existence may be expected, but in the more complete and severe forms mental changes are inevitable and sooner or later lead the affected person to a mental institution. Survival past early middle life is relatively uncommon.

TREATMENT

The nature of the condition precludes, as a rule, anything but palliative measures, and this fact explains why comparatively few patients have had any active treatment. Active treatment includes attempts at removal of diseased areas of the brain, ligation of the common carotid artery, tying or cauterizing the vessels entering into the formation of the pial nevus, freezing of meningeal adhesions or simple decompression. Good results have been claimed in a few instances with roentgen ray or radium therapy. Failures, including a high mortality rate in the surgical cases, appear to be as frequent as successes, and

37. Senear, F. E.: Parkes-Weber Syndrome, Arch. Dermat. & Syph. **41**:602 (March) 1940.

38. Gray, A. M. H.: Hemangiectatic Hypertrophy (Parkes-Weber), Proc. Roy. Soc. Med. **21**:65, 1928.

39. Pautrier, L. M., and Ullmo, A.: L'hémangiectasie hypertrophique de Parkes-Weber, Ann. de dermat. et syph. **10**:1195 (Nov.) 1929.

40. Weidman, F. D.: A Case of Extensive Angiomatous Nevus Associated with Congenital Hypertrophy of the Toes, Arch. Dermat. & Syph. **25**:735 (April) 1932.

41. Blumgart, H. L., and Ernstene, A. C.: Hemangiectatic Hypertrophy and Congenital Phlebarteriectasis, Arch. Int. Med. **49**:599 (April) 1932.

42. Gesell, A.: Hemihypertrophy and Twinning, Am. J. M. Sc. **173**:542, 1927.

even where amelioration is claimed it may be only temporary. Van Westrienen [43] stated the belief that no surgical intervention is warranted, because of the risk of severe hemorrhage. In assessing the value of any treatment it is also important to remember that spontaneous remissions of symptoms are fairly frequent. In cases of amentia, treatment is limited to symptomatic measures and mental hygiene, since no regression of the aplastic brain tissue is possible.

SUMMARY

A description is given of the main features of the Sturge-Weber syndrome. These include facial and pial nevus, calcification of brain substance, epilepsy, hemiplegia and glaucoma.

A case is reported in which nearly all the classic manifestations of this syndrome are shown.

Angiomas should be suspected in congenital disorders of the central nervous system, particularly if there is an associated vascular lesion of the skin or the mucous membranes.

30 North Michigan Avenue (2).

43. Van Westrienen, A.: Case of Cerebral Hemangioma, Maandschr. v. kindergeneesk. **3**:242, 1934.

PIGMENTARY DISTURBANCE FOLLOWING EXPOSURE TO MONOBENZYL ETHER OF HYDROQUINONE

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IN 1940, Schwartz, Oliver and Warren [1] reported the presence of depigmentation secondary to the wearing of yellow rubber gloves. The etiologic factor responsible for the leukoderma was traced to monobenzyl ether of hydroquinone (agerite alba®), an antioxidant used in the preparation of the rubber. After the original report, Schwartz,[2] in 1947, recorded several additional cases.

The purpose of this communication is to report further instances of this cosmetic disorder, including new data, to record the first case known to us in which hyperpigmentation resulted, to emphasize the probability that this dermatosis is more frequently encountered than the literature implies and to stress the fact that this disorder is not solely occupational in origin. Considering the diversified and numerous rubber products previously treated with monobenzyl ether of hydroquinone, the determination of the origin of this pigmentary disorder often might prove difficult or impossible.

The reports in this paper include those of 3 Negroes [3] employed in the manufacture of rubber dolls and of a white man exposed to neoprene, a synthetic rubber. However, in the 4 cases monobenzyl ether of hydroquinone was the antioxidant incorporated in the rubber to which these persons were subjected in handling the unfinished dolls or gloves. None of the patients had had an eruption or pigmentary disturbance preceding the disorder. In all the cases negative reactions followed patch tests with substances to which the patients were exposed, including the rubber itself; however, positive reactions were obtained with monobenzyl ether of hydroquinone.

From the Dermatologic Service, Beth David Hospital.

1. Schwartz, L.; Oliver, E. A., and Warren, L. H.: Occupational Leukoderma, Pub. Health Rep. **55**:1111 (June 21) 1940.

2. Schwartz, L.: Occupational Pigmentary Changes in the Skin, Arch. Dermat. & Syph. **56**:592 (Nov.) 1947.

3. These cases have been reported and were presented by one of us (E. T. B.) at a meeting of the New York Academy of Medicine in April 1948.

REPORT OF CASES

CASE 1.—W. C., a 36 year old Negro, after working at the same job for ten months, in April 1947, observed white spots on his face (fig. 1). About one month

Fig. 1.—Leukoderma involving most of the face.

Fig. 2.—Large depigmented patch covering part of the chest and axilla.

later similar lesions involved the hands and forearms. Gradually, new depigmented areas appeared; the preexisting ones increased in size, and the depigmentation became more vivid. There was no improvement after a three week vacation, during which the patient was free from exposure. The patient complained of loss of hair

on the forearms. He stated that there had been no dermatitis or erythema antedating the leukoderma. Furthermore, at no time had he been troubled with itching.

Examination revealed various-sized leukodermatous areas on face, hands and forearms. A patch test with monobenzyl ether of hydroquinone after forty-eight hours elicited a mild erythema with minute follicular vesicopapules in the area. Little itching was present.

Microscopic examination of an area of leukoderma revealed slight dilatation of vessels and a sparse infiltration of small round and wandering connective tissue cells throughout the upper part of the cutis. There was a moderate number of chromatophores, both perivascular and diffuse. Considerable interstitial edema of the upper and middle portions of the cutis was seen. Aside from pigmentary disturbance, the

Fig. 3.—Small areas of leukoderma scattered over the hands and forearms.

epidermis showed no important change. The pigment present in the margin of basal cells was localized in small areas, while most of this layer was free of pigment. Furthermore, the pigment in those areas where it was seen was less concentrated than it is observed to be normally in the skin of Negroes. There was no pigment in any other part of the epidermis.

CASE 2.—L. C., a 27 year old Negro woman, in September 1947, after having worked with rubber for five months, presented a pruritic eruption consisting of small patches of erythema on the face, chest, back, axillas, hands and forearms (fig. 2). The dermatitis disappeared in about one week; however, the previously involved sites began to show depigmentation. These white spots increased in size, and many coalesced to form large areas. This change was accompanied with gradual exaggeration of the loss of pigment. During a three week vacation, the patient noted no improvement but stated the belief that areas of uninvolved

skin on her face and chest had become darker and hyperpigmented. She complained of infrequent mild itching and noted that the hair on her forearms had changed from black to light brown.

Examination revealed depigmented areas of various sizes on the face, chest, back, axillas, hands and forearms. Many of these areas, particularly those of the axillas and forearms, were extensive; in fact, the forearms were practically white. A patch test with monobenzyl ether of hydroquinone resulted in a weakly positive response like that in case 1.

Microscopic study of a leukodermatous area revealed a picture essentially the same as that in case 1.

CASE 3.—A. S., a 25 year old Negro woman, in December 1947, after having handled rubber for five months, complained of pruritic erythematous lesions on the back of the hands, the forearms, the nape of the neck and the face (fig. 3). In

Fig. 4.—Hyperpigmentation on the hands and forearms.

about ten days the eruption disappeared, but the sites of the dermatitis began to lose pigment. This loss progressed until white patches resulted.

Examination of the patient revealed depigmented areas of various sizes on the hands, forearms, neck and face. Results of a patch test with monobenzyl ether of hydroquinone simulated those in cases 1 and 2.

On microscopic examination, a depigmented area presented a picture similar to those in cases 1 and 2. However, in this case, although pigment was missing in parts of the basal cell layer, the pigment-bearing areas were more extensive than were those in the aforementioned cases. The study of a spot that regained its pigment showed the inflammatory reaction and edema to be less pronounced and the chromatophores fewer. In line with normal findings, the entire basal cell zone contained pigment.

CASE 4.—S. A., a white man aged 36, in September 1946, complained of itchy red patches on the hands (fig. 4) following contact with neoprene (synthetic rubber) gloves for a period of eight months. Monobenzyl ether of hydroquinone had been used in the preparation of the neoprene. These patches gradually spread to involve

the forearms and the face. The erythema was followed by an increase in pigment until the affected sites became almost black. The patient complained of occasional pruritus in the so-called white spots.

On examination the pigmentation was seen to be mottled, and the white spots appeared depigmented, in contrast to the surrounding deeply pigmented areas. However, most probably the areas that appeared lighter were actually normal in color. A patch test with monobenzyl ether of hydroquinone resulted in erythema in forty-eight hours. The site of the patch test later showed small hyperpigmented spots, and a part of this area was removed for histologic study. As seen microscopically, the superficial vessels were dilated, and within the upper cutis was a sparse focal and diffuse infiltrate of small round and wandering connective tissue cells. The only important change within the epidermis was the presence of pigment in part of the basal cell layer.

COMMENT

In addition to the reported cases, 6 other cases with similar involvement were seen in the course of a routine inspection of the manufacturing plant. It was not possible to secure complete histories and make thorough examinations at the time; therefore, reports of these cases are omitted. Moreover, we know of several patients with this dermatosis who are under the care of other physicians. This observation indicates the relatively high frequency of this dermatosis, as well as the high incidence of the contacts with monobenzyl ether of hydroquinone.

In our series, the 3 Negro patients exhibited depigmentation, while the white man showed hyperpigmentation. We should like to call attention to the case, not reported here, of a white woman who was exposed to the aforementioned dolls and in whom an eczematous eruption developed, with no resultant pigmentary disturbance, after many months. Thus, this substance may give rise to allergic manifestations without resulting pigmentary disorder, or at times may lead to hyperpigmentation or, more commonly, to depigmentation.

The leukoderma in the case of the Negro man was apparently a primary occurrence. However, in the other 3 cases an inflammatory picture preceded the pigmentary disturbance. Schwartz [2] and Peck and Sobotka,[4] in their studies, observed the depigmentation to be primary. In fact, Schwartz concluded that monobenzyl ether of hydroquinone was the only chemical which resulted in depigmentation without a preexisting dermatitis. A secondary increase or decrease in the amount of pigment would not prove unusual, since pigmentary disturbance is observed fairly frequently after many dermatoses. Even if a theory of secondary evolution of the pigmentary change is accepted, there is, nevertheless, a high incidence of this change connected with monobenzyl ether of hydroquinone. In the event that there is no preceding erythema, the action of monobenzyl ether of hydroquinone would be unparalleled.

4. Peck, S. M., and Sobotka, H.: Effect of Monobenzyl Hydroquinone on Oxidase Systems in Vivo and in Vitro, J. Invest. Dermat. **4**:325 (Aug.) 1941.

But it is distinctly possible that there is always an erythema at the onset, which at times may be mild and overlooked by the patient. Such an oversight would be particularly likely in the case of a Negro.

In his report Schwartz stated that this dermatosis is a depigmentation of occupational derivation. He did note nonoccupational occurrences, in which leukoderma of the axillas followed the use of rubber shields. We have seen the loss of pigment on the chin of a young Negro woman [5] after contact with a rubber dam used in dental work. Although we are not aware of such cases, it seems likely that there should be a definite incidence among handlers of various rubber products, such as children with rubber toys and physicians with rubber gloves. This would exist whether or not perspiration were considered as a necessary factor.

We find it of interest to note that the areas of leukoderma were not confined to sites of exposure. Probably this characteristic is due to spreading both by absorption and by local peripheral extension. To some extent, too, these so-called nonexposed sites are actually areas of secondary exposure.

We agree with the observation of Schwartz that skins of Negroes exhibit the depigmentation more intensely than do skins of white persons. But this tendency is not remarkable, since it is known that the skin of the Negro reacts with pigmentary changes more readily and more frequently during the course of many dermatologic entities. Further, in accordance with the findings of Schwartz, at a later date the sites of patch tests became depigmented and the patients regained their pigment several months after separation from their work.

The fact that after forty-eight hours there was no reaction to patch tests with rubber is worthy of comment. Monobenzyl ether of hydroquinone caused a reaction in forty-eight hours. The negative response to rubber can be explained by the difference between the conditions of the patch test and the working conditions. The length of exposure, the amount of heat and perspiration and the size of exposed area, as well as other factors, are a few of the variants to be considered.

Probably the pilosebaceous apparatus may show involvement comparable to that of the glabrous skin. One of our patients observed a loss of hair on the forearms, while another noted that the hair on the forearms changed to a lighter color. Thus, in 1 case the hair showed a disturbance in development, while in the other it displayed loss of pigment. Peck, in experimental work with animals, caused depigmentation but found the hair bulbs unaffected. Weidman,[1] on microscopic study, described pigmentary disorder of the sweat glands in this dermatosis.

5. This case has been reported and was presented by W. Curth at a meeting of the New York Academy of Medicine in April 1948.

SUMMARY

Three cases of leukoderma following exposure to rubber treated with monobenzyl ether of hydroquinone occurring in Negroes are reported.

A case in which this chemical was responsible for hyperpigmentation in a white man is also reported.

We suggest the possibility of an erythema, perhaps mild and at times overlooked, preceding the alteration in pigment.

This dermatosis is more frequent than is commonly believed.

Examples of nonoccupational exposure to monobenzyl ether of hydroquinone are cited.

The microscopic changes correspond to the clinical picture.

The areas devoid of pigment were not limited to the sites of direct contact.

Restoration of the pigment followed elimination of the rubber as a contactant.

Pigmentary changes also involved the adnexa.

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LETTERER-SIWE DISEASE

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MINNEAPOLIS

IN 1924 Letterer [1] described a disease characterized by enlargement of the spleen and the liver, associated with anemia and a purpuric eruption. The patient in Letterer's case was an infant 6 months old, who died within four days after admission to the hospital. The disease was characterized histologically by a proliferation of large, pale reticuloendothelial cells which invaded and replaced the normal structure of the spleen, liver, bone marrow, skin and lymph nodes. Letterer reported his case under the title, "Aleukämische Retikulose (Ein Beitrag zu den proliferativen Erkrankungen des Retikuloendothelialapparates)." During the next nine years several similar cases were reported, and in 1933 Siwe [2] reported an additional case, of an infant 16 months old, and grouped all the cases together as representing a well defined entity. The term Letterer-Siwe disease was coined by Abt and Denenholz,[3] who considered the disease in great detail.

Letterer-Siwe disease is characterized by a distinct enlargement of the spleen and varying degrees of hepatomegaly. Osseous involvement may be present and, when not recognizable clinically, may be found in certain cases only by roentgen examination or at autopsy. The most constant finding, that of purpura, denotes a distinct hemorrhagic tendency, and as a rule there is secondary anemia of a progressive, nonregenerative type. The leukocyte count may be diminished or normal, and as a rule the platelet count and differential count are

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Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

From the Department of Dermatology, Samuel E. Sweitzer, M.D., Chief, and the Department of Pediatrics, A. V. Stoesser, M.D., Chief, Minneapolis General Hospital.

1. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**:377-394, 1924.

2. Siwe, S. A.: Die Reticuloendotheliose—eine neues Krankheitsbild unter den Hepatosplenomegalien, Ztschr. f. Kinderh. **55**:212-247, 1933.

3. Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of the Nonlipoid-Storing Macrophages; Discussion of So-Called Reticulo-Endothelioses, Am. J. Dis. Child. **51**:499-522 (March) 1936.

normal. There is also a generalized, painless and discrete enlargement of the lymph nodes. Letterer-Siwe disease occurs exclusively in infants, and neither familial nor hereditary tendencies have been noted. The duration of the disease is from a few weeks to several years. The onset is usually acute and the course downhill. The cause is unknown. The organs most commonly involved are the spleen, the liver, the lymph nodes, the bones, the lungs and the skin. Regardless of the organ involved, the microscopic picture is about the same and consists of a hyperplasia of pale, round, mononuclear histiocytes containing chromatic, eccentric nuclei.

The chief cutaneous sign of Letterer-Siwe disease is the tendency to hemorrhage, manifested mainly by petechiae or extensive purpura. Letterer's case presented a high grade purpura, and histologic examination showed hemorrhage in addition to necrosis of the epidermis and proliferation of large cells. The areas of most intense hemorrhage were in the papillary portion of the cutis, although there was a slight amount in the epidermis. The foci of proliferated histiocytes were of varying size and at times could be seen as broad sheaths in the papillary portion of the cutis. In some instances there was necrosis of the overlying epidermis. The cases of Guizetti [4] and Podvinec and Terplan [5] also presented petechiae, as well as extensive cutaneous hemorrhages. Siwe (1933), and later (1936) Abt and Denenholz, stressed the consistent tendency to hemorrhage in their discussion of these cases, which had been described under various titles, such as aleukemic reticulosis and acute or infectious aleukemic reticulosis or reticuloendotheliosis. There were no hemorrhagic lesions, however, in the cases of Schultz, Wermbter and Puhl,[6] Uehlinger [7] and Klostermeyer.[8] Necrotic, ulcerating angina, associated with petechial hemorrhages of the skin, was reported by Podvinec and Terplan. Under the title reticuloendotheliosis, Sweitzer, Winer and Cumming [9] (1939) reported a fatal case

4. Guizetti, H. U.: Zur Frage der infectiös bedingten Systemerkrankungen des reticuloendothelialen Apparates in Kindesalter, Virchows Arch. f. path. Anat. **282**:194-208, 1931.

5. Podvinec, E., and Terplan, K.: Zur Frage der sogennanten akuten aleukämischen Reticulose, Arch. f. Kinderh. **93**:40-55, 1931.

6. Schultz, A.; Wermbter, F., and Puhl, H.: Eigentümliche granulomartige Systemerkrankung des hämatopoetischen Apparates: (Hyperplasie des retikuloendothelialen Apparates), Virchows Arch. f. path. Anat. **252**:519-549, 1924.

7. Uehlinger, E.: Aleukämische Reticulose, Beitr. z. path. Anat. u. z. allg. Path. **83**:719-746, 1930.

8. Klostermeyer, W.: Ueber eine sogennante aleukämische Reticulose mit besonderer Beteiligung des Magen-Darmkanales, Beitr. z. path. Anat. u. z. allg. Path. **93**:1-10, 1934.

9. Sweitzer, S. E.; Winer, L. H., and Cumming, H. A.: Reticuloendotheliosis, Arch. Dermat. & Syph. **40**:192-199 (Aug.) 1939.

in a boy aged 3. There were lesions of membranous bones, the liver, the spleen, the lymph nodes and the skin. The eruption was composed of multiple brownish yellow papules on the scalp, neck, face, trunk and extremities, many of which lesions had a hemorrhagic tendency. Histologic examination of the skin showed an infiltrate of clear reticuloendothelial cells, which contained no lipid. In retrospect it seems that this was in all probability a case of Letterer-Siwe disease.

REPORT OF CASES

CASE 1.—B. J., a white female infant aged 3½ months, was admitted to the pediatric service of the Minneapolis General Hospital on July 15, 1947. The child weighed 5,270 Gm. and was 23 inches (58 cm.) in height. There was a history of "eczema" since birth, and within the previous few weeks the patient was said to have had diarrhea, with occasional bloody stools. There was a papular eruption

Fig. 1 (case 1).—Letterer-Siwe disease in a girl aged 3½ months. The posterior view shows seborrhea-like lesions of the scalp and an extensive hemorrhagic papular eruption on the trunk.

on the scalp, which had been present at birth, and at the age of 1 month a scaly eruption had been noted over the scalp, the chest, the back of the ears, in the creases of the neck, the axillas and the cubital and popliteal spaces.

The paternal grandfather and three aunts had had or had leukemia. The patient's sister, aged 18 months, was living and well.

The baby was referred to the hospital because of the dermatosis. The diagnostic considerations on admission were atopic and seborrheic eczema. Thick, yellow crusts were diffusely distributed over the scalp and, to a less extent, over the lower portions of the abdomen and on the legs. Reddish brown papules 1 to 2 mm. in diameter were interspersed among the crusted areas. After the patient had been in the hospital for two weeks, the liver became enlarged 2 fingerbreadths below the costal margin, and a large, firm mass was palpable in the splenic region. The patient was still passing many bloody and mucoid stools. One month after her admission all the cutaneous lesions became definitely hemorrhagic, and the postauricular and cervical nodes became enlarged. No generalized adenopathy

was present at this time, although the spleen had increased considerably in size. The patient's temperature varied from normal to 104 F.

Despite treatment with penicillin, succinylsulfathiazole (sulfasuxidine®), repeated blood transfusions, fluids administered intravenously and oxygen, the intense diarrhea continued, and the patient became increasingly weaker. She died on September 19, sixty-six days after admission to the hospital.

Laboratory Data.—The number of white blood cells varied from 6,000 to 11,000, with 55 per cent polymorphonuclear leukocytes and 45 per cent lymphocytes. The hemoglobin concentration, which had been 70 per cent on admission, gradually dropped to 29 per cent just before death. Serologic tests for syphilis gave negative reactions, and the urine showed no abnormalities. The reaction to the histoplasmin test (dilution of 1:100) was negative on August 6, and on the same day the reaction to the Mantoux test (dilution of 1:1,000) was also negative. On September 12, the blood cholesterol was 165 mg. per hundred cubic centimeters.

Fig. 2.—Anterior view of the patient shown in figure 1.

The gross diagnoses after autopsy were as follows: reticuloendothelioma; splenomegaly; generalized enlargement of lymph nodes; infiltration of the lungs; hemorrhagic crusted, cutaneous lesions on the face, chest and abdomen, and petechiae of the cecum and pericardium.

Histologic Observations.—A hemorrhagic papule from the thigh was removed with a cutaneous punch, fixed in formaldehyde solution U.S.P., dilute, embedded in paraffin and sectioned in the usual way. The tissues were stained with hematoxylin and eosin and with sudan III for lipids.

In sections stained with hematoxylin and eosin the outstanding pathologic changes, which were immediately obvious, were situated in the upper portion of the cutis, directly beneath the epidermis. Numerous loosely arranged reticuloendothelial cells, having large, irregularly shaped nuclei and eosin-staining cytoplasm, were present in this area. Because the cells were not densely packed, the entire affected zone assumed a foamy appearance. There were numerous erythrocytes and a few lymphocytes interspersed among the larger reticuloendothelial cells. The large monocytic cells showed no special tendency toward a perivascular arrangement but were situated in a bandlike focus, the lower

margin of which was well demarcated from the underlying normal connective tissue. At the upper margin, however, the infiltrate seemed to disrupt the epidermis in many places, so that there was no sharp line of demarcation between the infiltrate and the overlying epidermis, one seeming to fuse into another. There was definite thinning of the epidermis overlying the infiltrate. In the deeper portions of the cutis only nonspecific changes, such as moderate dilatation of the blood vessels, with surrounding lymphocytic infiltration, were seen. In sections stained with sudan III no abnormal deposits of lipids could be seen. Histologic examination of internal organs (Department of Pathology, Minneapolis General Hospital) showed that the mucosal layer of the intestine contained a large number of mononuclear cells with nuclei which were pale-staining and had fine chromatin patterns. These were regarded as hyperplastic reticulum cells.

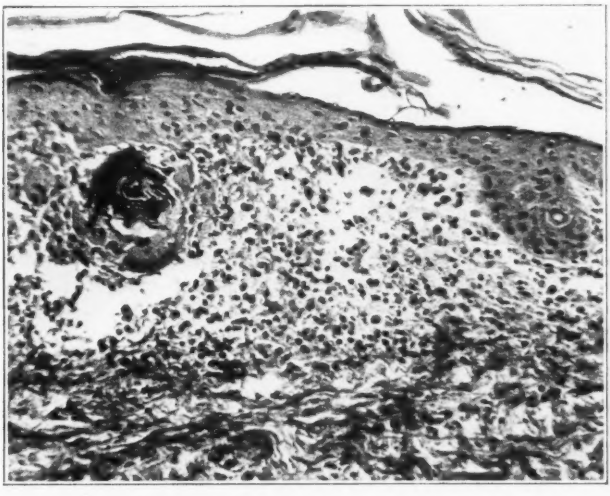

Fig. 3 (case 1).—Histologic features of the skin, showing foamy appearance of the upper portion of the cutis, with loosely arranged reticuloendothelial cells and erythrocytes.

A section from the right side of the skull showed complete destruction of bone, with replacement by fibrous tissue and a number of large, pale-staining mononuclear cells.

The normal structure of the bone marrow was replaced by large cells with a moderate amount of cytoplasm, containing round or oval nuclei with small clumps and fine strands of chromatin similar to that of the cells in other organs.

An identical infiltration was seen in the lungs, liver, spleen, lymph nodes, thymus and kidneys. No abnormalities were observed in the ovary, pituitary gland, heart, adrenal glands or pancreas.

In sections from a lymph node and the spleen stained with sudan III no deposits of lipid were seen in the large reticuloendothelial cells.

CASE 2.—S. K., a white female infant aged 9 months when examined in October 1947, had a swelling which appeared behind the left ear at the age of 5 months. The lesion had increased in size from that of a dime at the time of

its onset to about 5 cm. in diameter at the time of examination. A similar lesion had soon developed behind the right ear, and this too had gradually increased in size to about 4 cm. At the age of 7 months the patient's gums had become red, swollen and necrotic. The patient had no teeth. At the age of 8 months a crusted eruption appeared over the scalp, back, chest, abdomen and body folds. A few days before she was examined (October 22), the baby became feverish and irritable and took little nourishment by mouth.

Clinical Examination.—There was a diffuse, crusted eruption over the scalp. Exudation and crusting were also noted in the groins and the axillas. Numerous purpuric, reddish brown, papular lesions 1 to 2 mm. in diameter were diffusely distributed over the back, chest and abdomen. There was a firm, deeply situated, tender nodule behind each ear. The gums were swollen, congested, extremely red and in certain areas necrotic. A roentgenogram of the skull showed several areas of rarefaction in the parietal areas bilaterally and in the occipital region. General physical examination showed no other noteworthy changes. The liver, spleen and lymph nodes were not enlarged. Roentgenograms of the chest showed a bilateral pulmonary infiltration, rather diffusely distributed. Examination of the blood showed no abnormalities except moderate anemia and a leukocyte count of 90,100. The blood cholesterol was 127 mg. per hundred cubic centimeters.

Histologic Examination.—A biopsy was made of a hemorrhagic papule from the chest. Sections stained with hematoxylin and eosin showed essentially the same changes as were described in case 1. Sections stained with sudan III showed no abnormal deposits of lipid.

Course.—Within two weeks the cutaneous lesions had entirely disappeared and the general condition of the patient was greatly improved. The patient was discharged from the hospital later in October and when last seen in December 1947 was still in good general health.

COMMENT

Within recent years increasing attention has been paid to a group of reticuloendothelial diseases which includes Letterer-Siwe disease, Schüller-Christian disease and a third disorder known as eosinophilic or destructive granuloma of bone. Most of the articles devoted to this subject have been by pathologists, pediatricians, internists or orthopedists. Since cutaneous lesions, as well as visceral involvement, are prominent features of these processes, added attention should be given them by dermatologists. Farber,[10] Mallory [11] and Jaffe and Lichtenstein [12] have all made contributions which have helped to clarify the classification and relationship of these disorders.

Mallory suggested that Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma of bone were all manifestations of an identical underlying basic disease of the reticuloendothelial system.

10. Farber, S.: The Nature of "Solitary or Eosinophilic Granuloma" of Bone, Am. J. Path. **17**:625-629, 1941.

11. Mallory, T. B.: Medical Progress: Pathology; Diseases of Bone, New England J. Med. **227**:955-960, 1942.

12. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone, Arch. Path. **37**:99-118 (Feb.) 1944.

In a recent paper Bartels [13] expressed agreement with this view. If this basic reticuloendothelial disease manifests itself in infancy or early childhood, it appears in a form which is usually fatal and in which the lesions are widely distributed through both the soft tissues (especially the lymphoid tissues) and the skeleton. This is the so-called Letterer-Siwe type. The disease, however, may appear in older infants, in children or in adults, in whom it pursues a more chronic course. In this type the lesions are, again, not usually limited to the skeleton and tend to undergo collagenization and lipidization. In this type the prognosis is often serious because of the possibility of damage to the brain or the pituitary gland, but an estimated 30 per cent of the patients recover. Early descriptions of Schüller-Christian disease emphasized that diabetes insipidus, exophthalmos and lesions of the skull represented a triad of cardinal symptoms. On the basis of more recent studies, however, especially those of Rowland [14] and Epstein,[15] it has become obvious that in many cases of Schüller-Christian disease one or more of the cardinal symptoms may be absent and that involvement may occur in entirely different organs. The one feature common to all the various types is the histologic finding of reticuloendothelial (foam) cells containing cholesterol. It is thus apparent that Schüller-Christian disease presents a great diversity of clinical manifestations.

"Eosinophilic granuloma of bone" was the title which Lichtenstein and Jaffe [16] assigned in 1940 to a disease characterized by a single osseous lesion, which was regarded as inflammatory. Within the past few years there have been rather extensive descriptions, discussions and studies dealing with eosinophilic granuloma of bone. The disease occurs predominantly in children and young adults. Solitary lesions roentgenologically may simulate bone cyst, osteomyelitis or malignant growths, and the lesions cannot be distinguished from those occurring in Letterer-Siwe disease or Schüller-Christian disease. Practically any bone may be involved, with either single or multiple lesions. Constitutional symptoms are absent, although tenderness and pain over affected bones are often present. In most cases the lesions of eosinophilic granu-

13. Bartels, J.: Over het eosinophiele granuloom der beenderen, en het verband hiervan met de ziekte van Hand-Schüller-Christian en de ziekte van Abt-Siwe-Letterer, Nederl. tijdschr. v. geneesk. **91**:2578-2589, 1947.

14. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System: Correlation of Unidentified Group of Cases Described as Defects in Membranous Bones, Exopthalmos and Diabetes Insipidus (Christian's Syndrome), Arch. Int. Med. **42**:611-674 (Nov.) 1928.

15. Epstein, E.: Die generalisierten Affektionen des histiozytären Zellensystem (Histiozytomatosen), Med. Klin. **21**:1501-1504, 1925.

16. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of Case, Am. J. Path. **16**:595-604, 1940.

loma heal uneventfully after roentgen irradiation or curettage or the two methods. Histologically an abundance of histiocytes, with varying numbers of eosinophils, characterizes the osseous lesions.

As aforementioned, most observers within the past few years have felt that so-called Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma of bone should be grouped together as manifestations of a reticuloendotheliosis. One is certainly unable, by comparing the courses and symptoms of these conditions, to find concrete evidence that Letterer-Siwe disease and Schüller-Christian disease are distinct. Letterer-Siwe disease is almost invariably fatal, but it may run a more or less protracted course. On the other hand, though Schüller-Christian disease as a rule is more chronic, it can be rapidly fatal. Progressive anemia; a tendency to hemorrhage; enlargement of the spleen, liver and lymph nodes; osseous lesions, and fever are all symptoms which may be present in both types. Even the triad of symptoms (exophthalmos, diabetes insipidus and cranial lesions) may occur in either the Schüller-Christian type or the Letterer-Siwe type. The localization of the osseous lesions in the two types offers no good differential point, since either the flat or the long bones may be involved in either type. It is true, however, that the skull is more frequently affected in the Schüller-Christian type and the long bones or ribs in the Letterer-Siwe type. The cutaneous lesions in either type offer no important means of differentiation, since in both disorders the eruption tends to be hemorrhagic. This hemorrhagic tendency is more noticeable in the Letterer-Siwe type, whereas in the Schüller-Christian type the cutaneous lesions are more likely to be diffusely papular or seborrhea-like.[17] Bronze pigmentation and xanthomas have also been reported to be associated with the Schüller-Christian type.

The idea that the Schüller-Christian type is characterized by a storage of lipid in the reticulum cells cannot be regarded as an essential and usable means of differentiating this condition from other reticuloendothelial granulomas. Wallgren [18] demonstrated beyond doubt that in Schüller-Christian disease the reticulum cells may show large amounts of cholesterol-containing foam cells in certain organs, while in other organs these cells may be entirely absent. Thus it would seem that if a proliferation of reticulum cells can take place without a trace of local accumulation of lipid, Schüller-Christian disease can hardly be regarded as a primary disturbance of cholesterol metabolism and should no longer

17. Lane, C. W., and Smith, M.: Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schüller-Christian Disease), Arch. Dermat. & Syph. **39**:617-644 (April) 1939.

18. Wallgren, A.: Systemic Reticuloendothelial Granuloma; Nonlipoid Reticuloendotheliosis and Schüller-Christian Disease, Am. J. Dis. Child. **60**:471-500 (Sept.) 1940.

be closely allied with Niemann-Pick and with Gaucher's disease. It is worthy of note that hypercholesteremia is an inconstant feature of Schüller-Christian disease and when present can be regarded as a phenomenon secondary to proliferation of reticulum cells. Lipidization of the lesions in these disease systems seems to occur late in the course. In a few cases of a disease diagnosed as Letterer-Siwe disease lipidization has occurred if the duration has been more than a year.

Eosinophilic granuloma of bone has been linked with the two aforementioned types largely because the osseous lesions cannot be distinguished roentgenologically and the chief histologic features are almost identical. Curtis and Cawley [19] recently reported a case of eosinophilic granuloma of bone with cutaneous manifestation. The patient was a 16 month old girl who at the age of 8 months had presented an eruption similar to seborrheic dermatitis on the scalp. At about the same time, small, red, discrete papules appeared on the buttocks and about the genitalia, and erythematous, painful, eroded patches appeared in various parts of the mouth. Shortly thereafter, lesions similar to those on the buttocks and about the genitalia were noted on the soles and between the toes. After roentgen therapy, both the lesions of the bones and those of the skin healed over a period of several months. Microscopically the cutaneous lesions at first resembled a malignant process, being especially suggestive of reticuloendothelioblastoma. Detailed examination, however, revealed all cells of the infiltrate to be well differentiated, with an abundance of histiocytes and in places a great many eosinophils, a picture compatible with eosinophilic granuloma of bone or Letterer-Siwe disease.

So-called eosinophilic granuloma of the skin has recently been discussed by Buley,[20] Lewis and Cormia,[21] Weidman [22] and Lever.[23] This dermatosis is characterized by firm, red, bluish red or brownish red plaques or nodules, which may be ulcerated, smooth or verrucous. The lesions may occur on the face, the trunk or the extremities. The number of eosinophils in the blood has varied from 8 to 55 per cent.

19. Curtis, A. C., and Cawley, E. P.: Eosinophilic Granuloma of Bone with Cutaneous Manifestations: Report of Case, Arch. Dermat. & Syph. **55**:810-818 (June) 1947.

20. Buley, H. M.: Eosinophil Granuloma of the Skin, J. Invest. Dermat. **7**:291-300, 1946.

21. Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma: Theoretic and Practical Considerations Based on the Study of a Case, Arch. Dermat. & Syph. **55**:176-193 (Feb.) 1947.

22. Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. **55**:155-175 (Feb.) 1947.

23. Lever, W. F.: Eosinophilic Granuloma of the Skin: Its Relationship to Erythema Elevatum Diutinum and Eosinophilic Granuloma of the Bone; Report of a Case, Arch. Dermat. & Syph. **55**:194-211 (Feb.) 1947.

Microscopically there is a dense infiltrate in the cutis, consisting of eosinophils, lymphoctyes, monocytes, histiocytes, plasma, mast cells, giant cells and epithelioid cells. In most cases the patient is not constitutionally ill and the disease is apparently not malignant. Improvement or cure has been reported to follow roentgen therapy, excision or the administration of arsenic, although in other cases the disease has been slowly progressive or resistant to treatment. Nothing is known concerning the cause and pathogenesis of eosinophilic granuloma of the skin. Until more is known about the disease, it is unwise to make deductions regarding its relation to Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma of bone.

SUMMARY

A case of Letterer-Siwe disease is reported in a girl aged 3½ months, who presented an extensive, hemorrhagic, papular and seborrhea-like eruption. Death occurred at the age of 5½ months, and both the gross and the histologic observations at autopsy confirmed the clinical diagnosis of Letterer-Siwe disease. A second case, in a girl aged 9 months, was also observed. While the eruption was about the same as that in the first case, the course was relatively mild, the general health remaining unaffected at the time of writing.

We are in agreement with other observers who have stated the belief that Letterer-Siwe disease, Schüller-Christian disease and eosinophilic granuloma of bone are merely variants of a basic underlying disease of the reticuloendothelial system and that Schüller-Christian disease should be withdrawn from classification with the primary disturbances of lipid metabolism.

It is felt that until more is learned concerning eosinophilic granuloma of the skin it cannot be definitely classified.

1017 Medical Arts Building (Dr. Sweitzer).

345 Medical Arts Building (Dr. Laymon).

ABSTRACT OF DISCUSSION

Dr. Francis W. Lynch, St. Paul: Sweitzer, Laymon, McAfee and Walsh have described 2 cases to be added to the growing list of examples of Letterer-Siwe disease. The first is characteristic, but there may be room for doubt as to the nature of the second. There was no enlargement of the liver, the spleen or the lymph nodes. The period of observation was short—less than three months—and the white blood cell count of 90,000 was high enough that more prolonged observation might be desired, unless perhaps the authors regarded the external and microscopic cutaneous manifestations of the disorders sufficiently characteristic to allow definitive diagnosis.

The expressed opinion as to classification of the disease supports the generally accepted view of the pathogenic unity of Schüller-Christian "disease" and Letterer-Siwe "disease." One wonders whether we of the medical profession should con-

tinue to use such terminology or whether it might be better to speak of two types of the same disease, essential xanthomatosis, as Thannhauser urged. It is possible that we should advance faster by noting the similarities rather than the differences while attempting to delineate the disease and discover its nature and course.

As yet one can hardly say more than that this disorder is essentially a pathologic process of the reticuloendothelial system, a system which may have numerous and widely divergent clinical and pathologic manifestations. The differences in these manifestations are in striking contrast to the simplest pathologic processes observed in epithelial structures and in ordinary connective tissues, where a variety of causes tend to produce a limited number of variations in pathologic response. In the case of the reticuloendothelial system, at one or at different times a single agent can lead to a variety of responses, perhaps because the tissue normally has so many different functions. Are all examples of these "diseases" due to a single cause?

What is the true nature of this disorder? There is only slight evidence that it relates with the hematopoietic function as an "aleukemic reticuloendotheliosis," a term of insecure standing. There is no longer universal acceptance of the view that Schüller-Christian "disease" is primarily a disturbance of lipid metabolism, and Letterer-Siwe "disease" is much less likely to be so explained. Perhaps the reticuloendothelial tissues here have responded to an infectious agent. But, if so, what is its nature, and where is the positive evidence? In Letterer's case, in that of Podvinec and Terplan and in cases reported by others the disease was immediately preceded or initiated by acute infection. I described a similar sequence (but without osseous involvement) under the title of aleukemic reticuloendotheliosis (Cutaneous Lesions Associated with Monocytic Leukemia and Reticuloendotheliosis, ARCH. DERMAT. & SYPH. **34**:775-796 [Nov.] 1936; case 5, p. 783). Does the absence of osseous involvement establish a separate entity? Can these cases be clearly set apart from those of "reticuloendotheliosis" in older children or in adults? Dr. Sweitzer and his colleagues described an eruption like that characteristic of Schüller-Christian disease. Since disturbed lipid metabolism was not evident in the cases presented, may the seborrheic features of the eruption be due to disturbances of the carbohydrate metabolism, which is known to be influenced by the reticuloendothelial system? There are numerous possibilities deserving further and more exhaustive study in such cases. The authors have given considerable thought to these problems of etiology and pathogenesis, and I am sure that the group would like a statement of their opinions on these points.

DR. FRANCIS A. ELLIS, Baltimore: Dr. N. Chandler Foot, in his textbook (Pathology in Surgery, Philadelphia, B. Lippincott Company, 1945, p. 174), called the Letterer-Siwe disease a nonlipoid histiocytosis, a disease of the reticuloendothelial system in which the erythrocytes are ingested by the reticulum cells. In a patient recently seen in Baltimore, whose condition was diagnosed by Dr. John Wagner at autopsy, the diagnosis was suggested clinically by the purpuric eruption and by the fact that the disease was aggravated after each blood transfusion.

DR. S. E. SWEITZER, Minneapolis: I wish to thank Dr. Lynch and the other discussers for their remarks.

Dr. Ellis brought up the question concerning the relation of Letterer-Siwe disease to the reticuloendothelial system. I believe that this disorder should be grouped with the reticuloendothelioses.

SOAP, AND SOAP AS A VEHICLE FOR MEDICAMENTS

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NEW YORK

IT WAS quite inevitable that dermatologists, acutely aware of contact agents as a major cause of dermatitis, would eventually get around to a serious and persistent study of soap, to seek out its place in the general problem of simple dermatitis. This study has been done during the past decade, and we may now, with profit, critically survey the findings and conclusions to date.

It is recorded that the Romans brought back soap from the Germanic tribes. In the twenty centuries of the recorded consumption of what may be accepted chemically as soap, the product has been improved and perfected, not only chemically, but also clinically; that is to say, improvement has been made in terms of acceptability as a daily contactant for skin. The last quarter of the past century saw modifications of soap aimed at giving it functions other than mere cleansing. These modifications were essentially two. The first, with the advent of bacteriology and the awareness of infection, brought disinfectants into soap; and the second, a completely dermatologic recommendation for which the elder Unna was chiefly responsible, added topical medicaments to soap.

At the end of the second decade of this century, dermatologists in the United States were of the opinion that soap was a good and safe cleansing agent and that disinfectant chemicals might with advantage for special situations be incorporated in it. They were aware, too, of the European-sponsored recommendation that, because of the colloidal character of soap lather, soap could be medicated and the thick lather of the soap so medicated used as a topical remedy. American dermatologists, if I may judge from both the record and the practice, had been quite indifferent to the "soap problem" as a whole, having shown no enthusiasm for germicides in soap and completely ignoring (with the possible exception of soaps made with tar and sulfur) the idea of medicated soaps.

At that point American dermatologists seriously undertook to study the "soap problem" and came fortified with a modern dermatologic procedure and modern chemical concepts. I refer specifically

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to the "patch test," on one hand, and to the concepts of ionization states, on the other. What these studies, thus bolstered by modern approaches, accomplished can best be gathered from the advertising pages of our medical journals—a veritable flood of soap modifications and substitutes. I suspect that the fear that this flood might reach disastrous heights led to the organization of a rescue squad to give substance to the recent book, "The Medical Uses of Soap." [1]

Patch testing is now universally practiced by American dermatologists. I fear, however, that the strict necessity for standardizing procedure for use in the testing of different categories of substances is not so generally understood. The procedure for testing soap is still *sub judice*. Mildly positive reactions in tests with soap are still altogether too frequent to be accepted as meaningful. I should like to point out here that tests with surface tension–reducers (wetting agents)—and soap is one of these substances—involve the production of an increased permeability of the keratin, thus serving under the conditions of testing to minimize and undermine the normal protective value of the keratinous layer. This fact, I suspect, is pertinent in explaining most of the meaningless positive tests to soap. (In this discussion, I am ignoring the essential oils added to soap as fragrance. I believe that these oils, as allergens, are the most frequent single cause of trouble from soap mixtures per se and, further, that these oils are less likely to annoy when in mixtures not containing surface tension–reducers.)

I have the equivocal distinction of having introduced to dermatologists, about twenty-five years ago, the practice of measuring the hydrogen ion status of the cutaneous surface. Since then, more elaborate and persistent investigations by others have served to impress dermatologists with the "acid" character of the keratinous substance. There has arisen from this the philosophy of the "incompatibility" of alkaline mixtures for habitual application to skin, healthy or otherwise; and most cosmetic mixtures and soap have been the chief victims of this approach—and I say victims advisedly. Soap is necessarily alkaline in solution, and cosmetics, at least the most popular of them, are alkaline mixtures. However, both soap and cosmetics are still enjoying a healthy and extensive use. Dermatologists seek to keep keratin in a state of least reactivity, maximum impermeability and minimum swelling. Theoretically, these qualities are at the isoelectric point of the substance, which for keratin appears to be a p_H between 3.5 and 4.0. A p_H range of from 6.5 to 9.5, the upper limit of which is found with soap and alkaline cosmetics and the lower of which accompanies those substituted or modified products made to conform with the "acid mantle"

1. Fishbein, M.: Medical Uses of Soap: A Symposium, Philadelphia, J. B. Lippincott Company, 1945.

of the cutaneous surface, probably influences but little the reactive state of the cutaneous surface, which surface in its physiologic state is well removed from its isoelectric point. At any rate, experience proves the safety of mild alkalinity as habitually offered skin in the form of cosmetics and soap.

The fatty acid moiety of soap has received extensive and ingenious investigations via patch tests. In the light of the obvious safety in the universal practice of soaping the skin, these studies have given frankly terrifying and bewildering results. Erythematous reactions seem to be the rule rather than the exception, and persons with a totally healthy skin are quite as likely to react as are those possessed of a dermatitis. However, vesicular reactions as particularly induced by lauric acid or its sodium salt probably may be clinically meaningful. Statistically, all these studies have led to the deduction that the saturated, long carbon chain fatty acids, such as stearic acid, are the safest; the short carbon chain fatty acids, such as lauric acid, are the most irritating, and the unsaturated fatty acids, such as oleic acid, are on the dangerous rather than the safe side. On the basis of interpretations such as the foregoing ones, at least one "modified" soap mixture has been made available for clinical use. Furthermore, buffering the skin on the alkaline side in testing with the fatty acids has led to greater numbers of reactions of irritation.

It must have occurred to many dermatologists to ask the question: Are there categories of substances for which the patch test technic gives information deceptive rather than revealing? Have we come on one such substance in soap? In patch testing there is the dictum that one should approximate the situation present in the usual manner of exposure to the substance. When the time element is of crucial significance (soap is applied for a few moments at any single time of exposure), can a patch test adequately be modified to make a constant single twenty-four hour exposure the equivalent of several momentary exposures throughout that period?

An interesting commentary on both the alkalinity and the fatty acid phase of danger from soap is supplied by two types of clinical experience pertinent to this report. For several decades, at least, the favored topical application for hospitalized patients at the Skin and Cancer Unit in New York city has been a "Burow's emulsion," a stabilized emulsion made with olive oil, calcium hydroxide solution U. S. P. (lime water), wool fat (anhydrous lanolin), zinc oxide and talc, medicated with solution of aluminum acetate N. F. (Burow's solution). Its formula and the precise method of its compounding currently carry the name of Dr. Isadore Rosen, and most of the pharmacists in New York city who cater to dermatologists have acquired this formula

and knowledge of the method of preparation. I have taken the trouble to assure myself that this emulsion, made anywhere, is an alkaline mixture. Dermatologists are still all satisfied in their use of it in acute eczematous dermatitis.

I have for the last eight years been interested in the possibilities of ozonides [2] in topical remedies. Ozonides are formed by the direct addition of ozone at the point of double linkage in unsaturated fatty acids or their esters. The ozonide is highly unstable, constantly releasing elemental oxygen and in its degradation forming shorter chain acids and aldehydes. For clinical use, thus far only olive oil has been used as the base material for the manufacture of ozonides. The product, therefore, is essentially triolein ozonide in olive oil. Cronheim [3] cited the following materials as forming in these unstable ozonide mixtures in which an olive oil base is used: pelargonic aldehyde, pelargonic acid, ω-formylcaprylic acid, azelaic acid, caproaldehyde, caproic acid, malonaldehyde, formylacetic acid and malonic acid. Surely, this chemical picture, in the light of what has been revealed in studies of soap, should presage a high incidence of irritation from the use of ozonides. Experience emphatically denies that this high incidence exists.

I am convinced of the damage that soaping the skin may assist in producing on occasion, as I am of the inadequacy of the current explanations of how the insult occurs. I offer a concise statement of my conviction as to the essential factors underlying so-called soap damages to the skin. Soap must be used with water. Soap is a wetting agent encouraging the hydration of the keratin. The hydration of keratin reduces the elasticity of this albuminous material. Further, keratin, bloodless and in immediate contact with the weather, suffers variations in temperature over a wide range, and the colder the keratin, the less its elasticity. Keratin thus damaged will fracture when subjected to repeated tensions. True damage to the skin from soap is usually revealed on the dorsum of the hands—areas constantly exposed to the elements, most frequently wetted and under constant tension from the flexing of the fingers.[4] Water and cold, abetted by soap, produce this damage. And, as often as not, water and cold need no assistance from soap for the production of these unfavorable changes in the skin.

The clinical picture, for the most usual location of this simple damage, is common enough—the skin on the dorsum of the hands feels

2. Sharlit, H.: The Use of Ozonides in Dermatology, New York State J. Med. **46**:2147, 1946.

3. Cronheim, G.: Organic Ozonides as Chemotherapeutic Agents: Chemical Studies, J. Am. Pharm. A. (Scient. Ed.) **36**:274, 1947.

4. Sulzberger and Baer, in their chapters in "The Medical Uses of Soap," [1] recognize the importance of water in the effects discussed by the repeated use of the expression "soap and water" as an inseparable combination.

rough, appears dried out and is streaked with a myriad of tiny red lines (a reflection of the capillary bed through the fractured keratinous layer). The hand lotion industry seeks sustenance from this fact, and receives it because hand lotions effectively serve to minimize and allay this damage. That skin thus prepared through damage by hydration can more readily react with eczema to exogenous or endogenous noxae is not difficult to understand or to believe. The care of patients with eczema of the hands has been the bane of dermatologists. Unless I grossly misjudge the situation, this condition is still the challenge it always was and continues to serve as inspiration for further studies.

There is justification, I think, for recalling the two clinical experiences that stimulated my interest in modifying soap mixtures to seek a solution of the "soap problem." The first was the recurring complaint, known to all dermatologists, I am sure, of patients, particularly women, who insist that they must avoid cleansing the face with soap since it roughens the skin and leaves it dry and scaling and who thus continually use cleansing creams and as well daily indulge in the use of hand lotions. The other was the observation of the comparative rarity of dermatitis of the hands in barbers, who continually expose their hands to soap in preparing faces for shaving. Revealing to me was this observation of the barber's practice. The barber uses the minimum amount of water necessary to whip up the soap lather and removes the residual lather from his hands by milking it from hands and fingers, after which procedure he dries the hands with a dry towel. He avoids flushing the hands with a stream of water and has no fear of the persistent presence of soap on his hands.

Hydration of the keratin comes from the excess of water applied to the skin in soaping, which excess begins to become available after completion of the lathering. Limiting the amount of water used and using a soap that lathers abundantly serves to avoid the first step in damage to the skin from soap, namely, hydration of the keratin. With use of the proper type of soap, measured tests have disclosed that an adequate washing of the hands can be accomplished with as little as 10 cc. of water, provided that the excess lather is finally removed by milking the hand, as barbers do.

It was my impression that an oil-laden lather, if available, would simulate hand lotion mixtures, make it possible for one to cleanse with use of a minimum amount of water and offer a residual oil film on the skin after use. Some years ago I achieved the production of a soap able to meet these conditions and commented briefly on it in a report on the "soap problem."[5] More recently, opportunity was

5. Sharlit, H.: Soap and the Soap Problem, New York State J. Med. **43**:160, 1943.

afforded me to experiment more extensively in this field. A soap[6] superoiled with approximately 10 per cent of a vegetable oil, adequately hard as a cake and readily delivering an oily lather, has, where used, satisfied the demands of the skin that fears soap and has served safely to cleanse skin in the presence of dermatitis, provided flushing with water to remove the soap completely was continually avoided.

What I have here presented has led to my conviction that soap lather, and more especially oiled lather, is a completely safe application to skin, healthy or damaged. With this premise, justification exists for probing the possibilities of medicated soaps within whose lathers finely or, if you will, colloidally dispersed medicaments can be made available. Now afforded the opportunity to make such studies and, indeed, even to extend cooperation to those of my colleagues similarly interested, I look forward to investigations with medicated soaps, so enthusiastically offered by the elder Unna for use in dermatology.

The burden of this report has not been to deny the existence of occasional damage from soap, but, rather, to deemphasize the role the chemistry of soap plays in production of this damage and to stress the damage from water as used with soap. Soap, by extension, lends itself to a variety of modifications calculated to bring to the skin a soap solution for many minor cutaneous problems. One's cleansing habits are so thoroughly built around soap, its lather, and even its fragrance, that an adequate psychologic approach in dermatologic therapy requires a persistent recommendation of soap for satisfying this habit. If soap can serve to cleanse safely, and even to carry a medicament to an unhealthy skin, so much the better.

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ABSTRACT OF DISCUSSION

Dr. Isadore Rosen, New York: Dr. Sharlit has brought out some interesting facts regarding the causes of these therapeutically resistant cutaneous manifestations affecting the hands. Any suggestions that will help to control these recurrent dermatoses will be a valuable contribution to their therapy.

We dermatologists have all had disappointing experiences in the management of these eruptions. I am sure we have all tried every newly suggested therapeutic procedure, some measures with temporary success and satisfaction, only to be disappointed after a short while, when recurrences take place.

Undoubtedly, the introduction of the patch test has brought greater awareness of the extent and causal varieties of contact dermatitis. Too, it has served on occasion to reveal sensitivity to ointment bases by the persistent use of which eczemas have been maintained and aggravated. I think, too, that most of us in the profession have been aware that patch tests on occasion can lead to erroneous deductions. Dr. Sharlit raises the question of the deception that patch tests may play in connection with soap. He has described in detail how and why patients have the cutaneous manifestations. His reasons are logical. His emphasis on

6. Oilatum soap, The Stiefel Medicinal Soap Company, Oak Hill, N. Y.

water as at least a maintaining factor can be accepted. Dr. Sharlit's offered explanation of the manner in which water leads to what he calls fracturing of the keratin layer is interesting. Surely, the avoidance of water is helpful in most types of eczema.

There must, however, be other factors responsible for these symptoms. I am one of those who believe that a constitutional background is a contributing factor. In my experience I have found that irregularities in diet play an important etiologic role. Persons whose diets include foods which are highly seasoned or rich in fats—sauces and gravies, chocolates and nuts—show a decided improvement as soon as they are placed on a rational, bland diet. I believe that these factors of diet and constitutional background tend to alter the normal physiologic function of the skin itself, making it more liable to physical or chemical insults. Psychogenic and emotional upsets may also be mentioned as contributing factors, and climatic and seasonal changes play a role, especially in cold weather, when the tissues lose their elasticity because of reduced secretions and become more vulnerable to the mildest soap.

Dr. Sharlit's presentation, I am sure, will serve for many of us as worthy of further thought and an inspiration for future study.

Dr. Sharlit mentioned the use of Burow's emulsion as a highly satisfactory preparation for the treatment of these acute eruptions. While the ingredients of this emulsion are not new, the method of prescribing and preparing them is important. I have found that when one writes a prescription in the ordinary fashion, the pharmacist, no matter how well trained, delivers to the patient a product which, instead of being a real, soothing emulsion, may even act as an irritant.

After many attempts in pharmacologic technic, my associates and I arrived at the following prescription for Burow's emulsion:

Wool fat U. S. P.	30 Gm.
Olive oil	130 Gm.
Heat in a mortar and mix well and add	
Zinc oxide	30 Gm.
Talc	30 Gm.
Mix very well and add 6.0 cc. solution of aluminum acetate.	
Mix very well and add calcium hydroxide solution to make 300 cc.	

Dr. Marion Sulzberger, New York: Certainly, considering the substances with which Dr. Sharlit's excellent paper deals, namely, soap and water, and the types of cutaneous diseases and cutaneous damage concerned, it is my opinion that nothing more important has come before us at this meeting. I suppose that soap and water is the most used of all external applications to the human skin, and the group of diseases in which the skin has been reputed to have been damaged by soap and water embrace by far the commonest diseases which dermatologists are called on to treat. Except in some minor details, I am in agreement with everything that Dr. Sharlit said and wish only to emphasize a few of the points that he has made. The most important is that patch testing with the usual, accepted technic is useless in the evaluation of substances which act in ways other than the mechanism of allergic hypersensitivities of the eczematous type. The patch test certainly cannot be used to gage the direct effects of acids or of alkalis on the skin. I know of no way in which one can standardize the patch tests with soaps to make the results of significance in relation to the effects of alkali or free fatty acid. Dr. Milton Winternitz, Dr. David P. Barr, Dr. R. L. Baer, my other collaborators and I were faced during the war with the problem of ascertaining in advance whether certain races, groups or persons were cutaneously hypersensitive to vesicants, such as mustard gas (2-chloroethyl

sulfide). Four years of work showed us that we were not able to use patch tests to discover hypersensitivity to the direct primary vesicant effect of mustard gas but were able to use quantitative patch tests in persons who had become allergic to this chemical. I believe that if one wants to find out whether a person's skin is hypersensitive to a vesicant, such as an alkali or an acid, one must use some such technic as Burckhardt's method, which consists essentially in discovering whether or not the skin possesses a normal capacity for neutralizing alkalis or acids at its surface. This has proved of value. In short, one must at present confine the use of patch tests to the study of eczematous hypersensitivities. I think one can find out whether or not a person is sensitive in allergic eczematous fashion to the essential oils, perfumes and materials of that kind in soaps by diluting them and performing controlled and quantitative patch tests; but one cannot conclude from the results just what the soap and water will do clinically. The mechanisms of the damage by soap and water are as yet largely unknown. They are surely more complex than just damage by alkali and fatty acid. Dr. Sharlit's idea is probably a great addition to our thinking about the mechanisms concerned and well worth careful study as indicating one more possible factor by which soap and water may initiate, aggravate or perpetuate certain dermatoses.

Dr. Francis Ellis, Baltimore: Several of the Baltimore men suggested that I ask Dr. Sharlit whether the soap substitutes on the market are of much value in the treatment of patients with dermatitis due to soap and water. We have found that very few patients are benefited by the use of these soap substitutes recommended for the hands, clothes and dishes.

Dr. Joseph Klauder, Philadelphia: Dermatologists are rightly concerned not only with soap employed in cleansing the skin but also with all detergents used for this and other purposes, if these agents contact the hands of industrial workers.

It is apparent that soap—not merely toilet and bathing soap but also soap used for other purposes—is being displaced by an ever increasing number of nonsoap detergents, the so-called wetting agents. This notably applies to the washing of dishes, since there are about ten nonsoap compounds that are well advertised for this purpose. Similar compounds are being used for other purposes, such as washing windows and automobiles.

The effect on the skin of so-called wetting agents used as detergents and familiarity with such compounds are important to the dermatologist.

One cannot arbitrarily state that soap is or is not harmful to the skin without making qualifications. Soap is such a universal contactant of the skin that it is obvious that it is not harmful to a considerable number of persons. The universal use of soap is comparable to that of tobacco and alcohol, and likewise it may, in certain circumstances, exert a harmful action.

In a general way, in consideration of the alkalinity of soap and the acid reaction of the skin, it may be stated that soap is not compatible with the normal or the abnormal skin. To my knowledge, no one has disproved the results of the studies of Burckhardt concerning the loss of function of the skin to neutralize alkali in explaining dermatitis arising from exposure to alkaline substance. Considerations of these studies are not favorable in establishing soap, an alkaline substance, as an ideal detergent for the skin.

Dr. Herman Sharlit, New York: Thank you for the discussion.

NODULAR SUBEPIDERMAL FIBROSIS (DERMATOFIBROMA VERSUS HISTIOCYTOMA)

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THIS article is based on clinical and pathologic studies of 95 patients who had 1 or more lesions of nodular subepidermal fibrosis.

Unna,[1] in 1896, first described the condition as "fibroma simplex." It has become widely known as "dermatofibroma lenticulare" [2] or as "nodular subepidermal fibrosis." [3] For many years a fibroblastic, and possibly traumatic, origin of the condition was accepted. However, in articles published from 1931 to 1933, Woringer and his associates [4] questioned the fibroblastic origin of all these lesions and described what Woringer believed formed a separate entity under the title "histiocytoma." He and his associates found phagocytic reticuloendothelial cells. Their observations were supported by the studies of Senear and Caro [5] with the use of vital stains. More recently, in 1943, Gross and

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Abstract, with additions, of the thesis submitted by Dr. Rentiers in January 1946 to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

1. Unna, P. G.: The Histopathology of the Diseases of the Skin, translated by N. Walker, New York, Macmillan & Co., Ltd., 1896.

2. Schreus, H. T.: Dermatofibroma lenticulare: Fibroma simplex (Unna); Noduli cutanei (Arning und Lewandowsky), Arch. f. Dermat. u. Syph. **161**:456-461 (July) 1930.

3. Michelson, H. E.: Nodular Subepidermal Fibrosis, Arch. Dermat. & Syph. **27**:812-820 (May) 1933.

4. Woringer, F.: Histiocytome xanthélasmisé du Mollet, Bull. Soc. franç. de dermat. et syph. **38**:1401-1405 (Nov.) 1931. Woringer, F., and Kviatkowski, S. L.: L'histiocytome de la peau, Ann. de dermat. et syph. **3**:998-1010, 1932. Pautrier, L. M., and Woringer, F.: L'histiocytome de la peau, Bull. Soc. franç. de dermat. et syph. **40**:1659-1662 (Dec.) 1933.

5. Senear, F. E., and Caro, M. R.: Histiocytoma Cutis, Arch. Dermat. & Syph. **33**:209-226 (Feb.) 1936.

Wolbach [6] described a series of cases similar to those described by Woringer and his associates but advanced the belief that the nodules were in reality a form of sclerosing hemangioma. Thus, at the present time there exist three theories as regards the group of lesions originally designated "fibroma simplex."

Those who believe the histiocytoma a separate entity would interpret the histiocyte to be the basic cell of the nodule. Arnold and Tilden [7] suggested that this theory would place the histiocytoma in the xanthoma group. In this view they were further strengthened by the finding of a high familial incidence of diabetes mellitus and hypertension in the cases which they reviewed. Civatte; [8] Weissenbach, Cailliau and Martineau,[9] and Nicolas [10] regarded the histiocyte as a forerunner of the fibroblast; thus, to them the phagocytes present in some nodules of fibroma simplex represented an "arrest in normal growth and development" of a fibrotic nodule. Gross and Wolbach, having demonstrated to their satisfaction the origin of the phagocytic cells from the endothelium of the numerous vascular channels present in their cases, expressed the belief that the lesions are a variety of sclerosing hemangioma. Sweitzer and Winer [11] and Stecker and Robinson [12] attached little importance to the reticuloendothelial cells, expressing the belief that they are wandering or invading histiocytes engaged in phagocytosis of cellular debris and hemorrhagic areas in the fibroblastic nodules. Because of these widely divergent views, this study was undertaken.

CLINICAL STUDY

Our study is based on a total of 95 patients who had lesions diagnosed clinically as dermatofibroma or histiocytoma. Of this group 51 patients were female and 44 male. There was no racial predilection. The ages of

6. Gross, R. E., and Wolbach, S. B.: Sclerosing Hemangiomas: Their Relationship to Dermatofibroma, Histiocytoma, Xanthoma and to Certain Pigmented Lesions of the Skin, Am. J. Path. **19**:533-551 (July) 1943.

7. Arnold, H. L., Jr., and Tilden, I. L.: Histiocytoma Cutis: A Variant of Xanthoma; Histologic and Clinical Studies of Twenty-Seven Lesions in Twenty-Three Cases, Arch. Dermat. & Syph. **47**:498-516 (April) 1943.

8. Civatte, in discussion, Bull. Soc. franç. de dermat. et syph. **40**:1273-1275 (July) 1933.

9. Weissenbach, R. J.; Cailliau, F., and Martineau, J.: Histiocytomes de la peau à triple potentialité manifestée: fibrocytaire, xanthomateuse et pigmentaire, Bull. Soc. franç. de dermat. et syph. **42**:344-347 (Feb.) 1935.

10. Nicolas, in discussion, Bull. Soc. franç. de dermat. et syph. **41**:578 (March) 1934.

11. Sweitzer, S. E., and Winer, L. H.: Fibrotic Nodules of the Skin, Arch. Dermat. & Syph. **45**:315-327 (Feb.) 1942.

12. Stecker, J. F., and Robinson, W. L.: Dermatofibroma, Arch. Dermat. & Syph. **43**:498-503 (March) 1941.

the patients varied from 18 to 71 years. The lesions were found most frequently (in 27 cases) in patients between the ages of 40 and 50 years. Duration of the nodules varied from two months to forty-eight years. Twenty of the 95 patients had 1 or more nodules of more than twenty years' standing. Multiple nodules were frequent; 21 patients exhibited from 2 to 5 lesions each.

All nodules were round or ovoid, firm and easily palpable and varied from 0.5 to 3 cm. in diameter (fig. 1). While most formed a domed, smooth elevation above the surrounding skin, a few were found to be slightly depressed and surrounded by a shallow, moatlike furrow. All were freely movable and firmly attached to the overlying epidermis but free of deep fascial attachment. The color varied from the usual dusky brown to a pale ivory hue. Several lesions imparted a light yellow shade to the overlying epidermis, while 2 of this series might easily

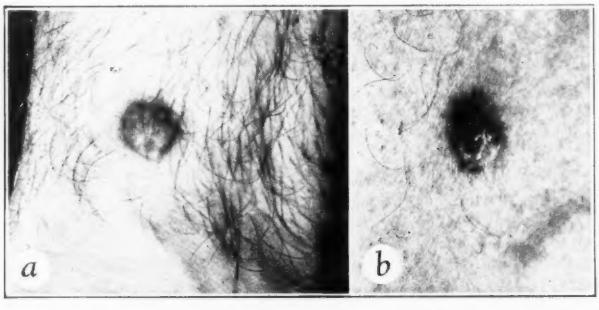

Fig. 1.—(*a*) Dermatofibroma: a firm, single, yellowish brown nodule of thirty years' duration, situated on the lateral aspect of the lower part of the left leg. There was no evidence of lipids or hemosiderin on histologic examination. (*b*) Histiocytoma: a single, bluish black nodule of fifteen years' duration, in the right popliteal space, clinically simulating an early melanoepithelioma. Deposition of lipids and hemosiderin in foam cells and histiocytes was demonstrated histologically.

have been mistaken for melanomas because of their deep blue-black coloring. Cases of pseudomelanotic lesions of this type have been reported frequently.[13]

13. Diss, M. A.: Histiocytome hémosidérinique pseudomélanique de la peau, Bull. Soc. franç. de dermat. et syph. **45**:1903-1907 (Nov.) 1938. Alkiewicz, J., and Suwalski, T.: Sur les rapports entre l'histiocytome et le dermatofibrome de Darier-Ferrand, Rev. franç. de dermat. et de vénéréol. **15**:195-210 (May) 1939. Montpellier, Méchin and Laffargue: Histiocytome noir de la peau, Bull. Soc. franç. de dermat. et syph. **46**:733-734 (May) 1939. Dobkévitch, S., and Ferreira Marques, M.: À propos de deux cas d'histiocytomes pigmentés, ibid. **46**:1388-1391 (July) 1939. Bernstein, J. C.: Hemosiderin Histiocytoma of the Skin, Arch. Dermat. & Syph. **40**:390-396 (Sept.) 1939.

All investigators have agreed that the extremities are most frequently involved, and in this series the incidence of distribution of lesions was as follows: lower extremity, 59; upper extremity, 37; trunk, 21; face and neck, 3; fingers, 2, and scalp, 1.

While a majority of our patients had paid little attention to the development of the nodules, 18 were able to state that growth had occurred during the first year only, after which the nodule had remained stationary or, in a few cases, had receded somewhat in size. Seventeen patients noted a gradual increase in size of the lesion, while 8 gave a history of recent sudden enlargement of the nodules. Only 1 patient had observed intermittent periods of growth of the lesion, these periods having invariably followed trauma to the site.

Symptoms were observed in 11 cases. In 4 cases there was a complaint of mild pruritus, while in the remaining 7 cases there was repeated ulceration and bleeding of the lesions following trauma. A history of injury preceding the appearance of the nodule was obtained in 21 of the 95 cases studied. Injury in 5 cases was of a piercing nature (in 1 the nodule occurred at the site of scarlet fever immunization). In 8 cases the lesions followed a scraping injury, in 3 cases they occurred at the site of irritation from articles of clothing, while in 5 they were preceded by the development of an inflammatory papulopustule.

In view of the recent work of Arnold and Tilden,[7] and of Portugal, Fialho and Miliano,[14] search for possible associated systemic conditions was carried out in all cases.

Sixty-eight of our patients appeared to be completely normal on general examination. In others the evidence of systemic disease seemed merely coincidental. Hypertension was found in a total of 9 patients, arteriosclerosis obliterans with intermittent claudication in 1, diabetes in 2, obesity in 10 and a varying miscellaneous group of systemic diseases in 10. The values for blood plasma lipids determined in 6 cases of dermatofibroma were within normal limits except in the case of arteriosclerosis obliterans, in which an increase in cholesterol was, of course, anticipated. Determination of blood plasma lipids in 4 cases of histiocytoma gave essentially normal results except in 1 case in which there was slight elevation of the values for total lipids and lecithin but essentially a normal value for cholesterol. There was no evidence of systemic disease in this case. One would anticipate definite elevation of the values for blood plasma lipids if either dermatofibroma or histiocytoma were related to xanthoma tuberosum, as Arnold and Tilden suggested.

14. Portugal, H.; Fialho, F., and Miliano, A.: Histiocitomatosis gigantocitaria generalizada, Rev. argent. dermatosif. **28**:121-144 (June) 1944.

HISTOPATHOLOGIC STUDY

One hundred and one lesions were removed from the 95 patients under study. All nodules were examined with hematoxylin and eosin, Van Gieson's connective tissue stain, elastin H, Mallory's potassium ferrocyanide stain and Becker's modification of the silver nitrate stain for melanin. The lesions of an additional 20 patients were examined with the Bodian stain for nerve fibrils. Frozen sections from nodules in 27 cases were studied with sudan III.

For simplification and purposes of description, the nodules were divided arbitrarily into two groups: (1) those comprised entirely of fibroblastic elements and (2) those in which reticuloendothelial cells were observed.

Group 1 comprised a total of 66 lesions answering in all detail the description of dermatofibroma lenticulare (fig. 2). All nodules of this group were observed to be made up of regularly shaped spindle cells arranged in parallel, intertwining and anastomotic bands. The lesions occupied the upper two thirds of the cutis, had complete absence of a limiting capsule and showed no tendency to encroach on the subcutaneous tissue. In all but the largest lesions, a narrow band of normal cutis separated the nodule from the basal layer of the epidermis.

The individual cells of the nodule revealed a striking similarity in size, shape and structure. All cells were of delicate spindle shape, with finely tapered ends from which collagen fibrils emanated to fill the intracellular gaps. The cellular protoplasm was clear, moderately abundant and delimited by a fine cell membrane of regular contour. The ovoid nucleus was centrally located, its long axis closely paralleling the long axis of the cell. Nucleoli were usually single and easily discernible. The nucleus was rich in dark-staining chromatin strands and rarely exhibited vacuolation.

Elastic tissue was entirely destroyed in all but 9 lesions. In these 9, a few fragments of clumped elastic strands were noted about the blood vessels at the periphery of the nodule. Evidence of phagocytic activity was entirely lacking. No histiocytes, foam cells or Touton giant cells were noted. Stains for iron gave negative results in all cases, and in 10 cases in which frozen sections were stained with sudan III no deposits of lipids were found. Sections of 10 lesions stained by the Bodian method failed to reveal the presence of neurofibrils, so that the possible confusion of the lesions with neurofibromatosis (von Recklinghausen's disease) was ruled out.

Atrophic remnants of coil and sebaceous glands were seen in 20 of the 66 lesions studied. In 5 of these 20 lesions, a dense lymphocytic and plasma cell infiltrate occurred about the atrophic remnants. In only 1 lesion, however, was the infiltrate so pronounced as to give the

histologic picture of granuloma. In this case, a foreign body giant cell reaction had occurred. Mitotic figures were never present in pathologic number. Though most nodules revealed only occasional single-

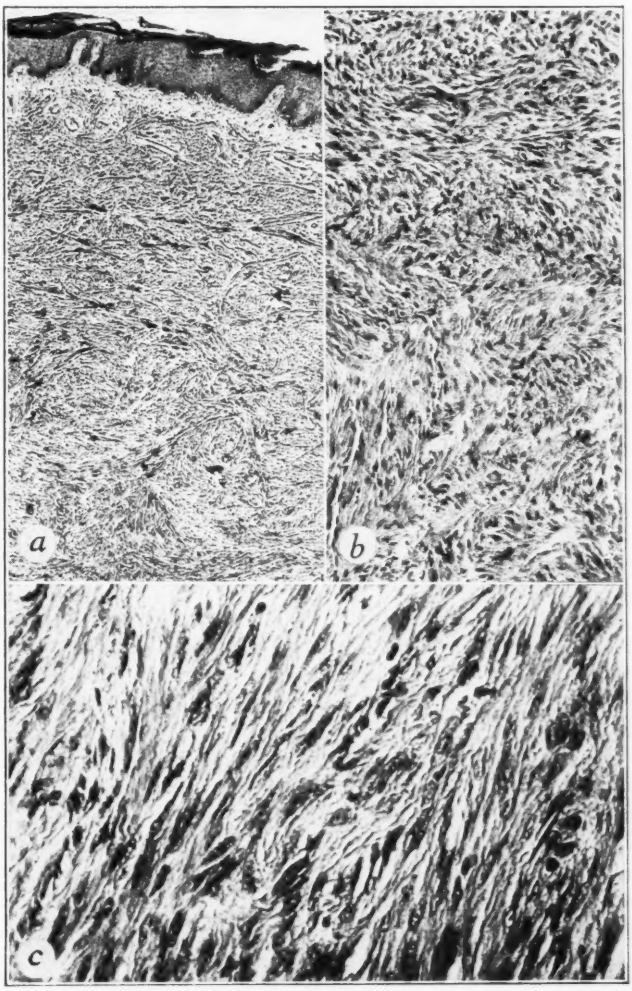

Fig. 2.—Dermatofibroma (hematoxylin and eosin stain). (*a*) Fibrotic nodule separated from normal epidermis by a flat band of normal cutis (× 30). (*b*) Section from same nodule as that in *a*, showing interlacing, regular bands of fibroblasts, relative absence of vessels and increase in collagen (× 110). (*c*) Section from same nodule as that in *a*. Note the uniformity of cellular structure and characteristic spindle-shaped fibroblasts (× 400).

layered capillaries, 4 of the lesions exhibited such pronounced vascularity as to render them comparable to the group of lesions described by Gross and Wolbach as "sclerosing hemangioma." However, unlike the latter workers, we were unable to demonstrate evidence of phagocytosis, endothelial proliferation or endothelial giant cell formation in this group of dermatofibromas.

The epidermis overlying the lesions was normal in most cases. Mild acanthosis and papillomatosis were occasionally encountered, while in 3 lesions the epidermis revealed general thinning, with loss of rete pegs. Increased deposition of melanin immediately above the nodule was found in 13 cases, while in 3 cases there was complete lack of pigment. The only changes noted in the band of cutis above the fibroblastic nodule were slight dilatation of the capillaries and frequently a mild degree of perivascular lymphocytic infiltration.

Two nodules deserve special mention in view of the fact that evidence of collagenous degeneration was prominent. In 1 of these nodules extensive deposition of calcium had occurred and the calcium was present in irregular deposits throughout the area of collagenous degeneration.

Group 2 was comprised of 35 of the 101 lesions studied and included all lesions in which reticuloendothelial elements were discovered (fig. 3). The amount of reticuloendothelial tissue present in the nodules varied considerably in individual cases. By far the most prominent feature, however, was that of scattered foci, or "nests," of histiocytic cells interspersed in irregular fashion about the body of the nodule. These areas were most commonly ovoid or crescentic, less densely cellular than the surrounding tissues and invariably located close to or surrounding a vessel. Collagen was reduced in these areas to a few attenuated strands. The reticuloendothelial nature of the cells was ascertained in all lesions by the presence of many areas in which a transition from the histiocyte to the foam or "Chambard" cell [15] had taken place or was occurring. In the majority of the foam cells, cholesterol clefts in the cellular protoplasm asserted the phagocytic nature of the cell. Further evidence as to the origin of these nests or whorls was obtained by differential staining. In 33 lesions with the use of Mallory's potassium ferrocyanide stain, blue granules of hemosiderin could be discerned intracellularly. In an additional 17 lesions, on which staining of frozen sections with sudan III was done, intracellular lipids were demonstrated. Whereas a few of the lesions in this group were predominantly of reticuloendothelial makeup, the majority of the nodules were predominantly fibrous in structure and differed in no other respect from the previously described lesions in group 1.

15. Lévy, G.: Xanthélasma et xanthome, Ann. d'anat. path. **2**:247-282 (May) 1925.

Like the lesions of group 1, those of group 2 were seen to occupy the upper two thirds of the cutis and exhibited no invasive tendency. The lesions were all ill defined, and not encapsulated, and merged

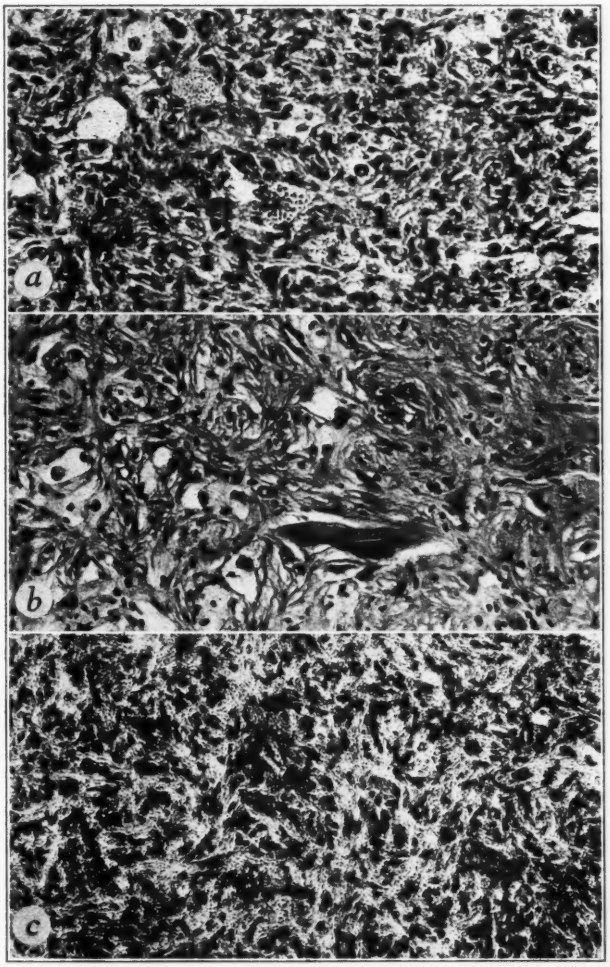

Fig. 3.—(*a*) Histiocytoma. Large foam cells containing granules of hemosiderin are visible. Note the disorderly arrangement of the cells (hematoxylin and eosin stain, × 200). (*b*) Histiocytoma. Note the sharp differentiation of typical xanthoma or foam cells on the left and the fibroblastic cells on the right. This lesion revealed many isolated groups of lipid-storing cells surrounded by fibroblasts (hematoxylin and eosin stain, × 200). (*c*) Histiocytoma (from same nodule as that in figure 1 *a*), showing intracellular deposits of lipids, photographing black (sudan III stain, × 200).

gradually with the surrounding normal cutis. Elastic tissue was entirely absent in 16 lesions and moderately diminished in the remaining 19. In 14 lesions atrophic remnants of coil and sebaceous glands were seen in the nodule, while in 2 lesions atrophic hair follicles were present. The changes in the epidermis above these nodules were essentially those described in group 1. As in group 1, a narrow band of cutis existed between the nodule and the basal layer of the epidermis, and in this band capillary dilatation and perivascular infiltration were frequently observed.

The vascular component of the nodule was observed to vary within wide limits (fig. 4). Whereas the majority of the nodules exhibited but few fine vascular channels, usually consisting of a single layer of endothelial cells, several harbored one or more larger arterioles with accompanying venule and but few small-calibered vessels. Still others were richly vascular, the vessels being for the most part of capillary nature. In only 2 lesions did the degree of vascularization of the tissue and the presence of many newly formed vascular channels suggest the change noted by Gross and Wolbach as seen in sclerosing hemangioma. In both these lesions endothelial proliferation was present, and scattered giant cells were observed in areas of lipid deposition in 1 of them. Bodian stains on 10 lesions of this group did not reveal neurofibrils.

In another 2 lesions areas of dense inflammatory infiltrate were noted. Both lesions exhibited this change about large vessels, while in 1 lesion the change had occurred in an area of massive hemorrhage about a ruptured vessel. In the latter lesion many plasma cells, lymphocytes and polymorphonuclear leukocytes and foreign body giant cells had collected to form a zone similar to that described by Michelson as resembling a true granuloma.

MULTIPLE LESIONS

Brief reference to those cases in which more than 1 lesion was available for histologic study should be made. In 1 case in this series a total of 4 separate nodules was furnished, 3 of which were from the lower extremities and 1 from the buttock. Two of the former contained multiple collections of reticuloendothelial cells, many of which revealed phagocytosis of both lipid and hemosiderin. In 1 of the 2 nodules many giant cells of the foreign body type were noted. The other 2 lesions were of purely fibrous texture, and no areas of phagocytic activity were seen.

In a study of 3 additional cases in which 2 lesions each were removed, the lesions in the first case exhibited "histiocytic" nests,

while those in the second and third cases were a purely fibromatous nodule and a nodule in which phagocytic histiocytes and foam cells could be demonstrated.

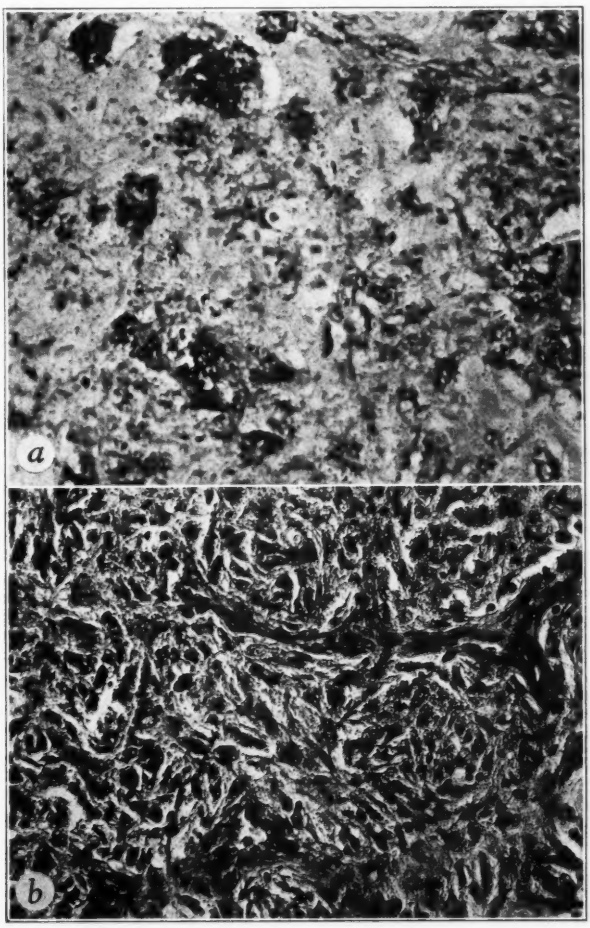

Fig. 4.—(*a*) Pronounced deposition of hemosiderin, photographing black, in typical foam cells (Mallory's potassium ferrocyanide stain, × 400). (*b*) Sclerosing hemangioma (histiocytoma). The lesion, of two months' duration, occurred on the left leg of a woman aged 62 and clinically suggested histiocytoma or hemangioma. Note the vascularity of the tumor and the intracellular and extracellular deposition of hemosiderin, photographing black. The increase in capillaries approximates that of Gross and Wolbach's concept of sclerosing hemangioma (Mallory's potassium ferrocyanide stain, × 250).

VITAL STAINING STUDIES

The lesions in 10 patients not included in the original series were studied by means of a modification of the method outlined by Senear and Caro (fig. 5). In 3 of the 10 cases one-half the nodule was removed with the use of local anesthesia, and at the time of the operation 15 minims (1 cc.) of a 10 per cent solution of saccharated ferric oxide was injected at the base of the remaining one half. This injected portion was removed surgically in seventy-two hours. Injections were also made in control areas of normal skin and the areas examined in seventy-two hours in all 3 cases. In the remaining 7 cases the entire lesion was removed forty-eight hours after injection of the ferric oxide.

Of the 10 nodules studied in this manner, 2 were observed to contain reticuloendothelial derivatives, that is, nests of histiocytes and foam cells in the tumor tissue. Both these nodules revealed, on preinjection study, intracellular deposition of lipids and iron.

After the injection of iron, the 2 lesions which had revealed phagocytosis of iron and storage of lipid previous to injection were observed to contain much greater quantities of the former, both intracellularly and extracellularly. In 1 of these nodules the injected iron appeared in appreciably increased quantities within the lipid-storing cells and cells immediately adjacent thereto. Thus, these cells could be seen even more clearly as localized collections. Between the nests of phagocytic cells were wide bands of apparently unchanged cells, which exhibited no inclination to share in the phagocytosis. In the second lesion the phagocytic cells did not form definite collections, but were noted to be filled with iron granules scattered evenly throughout the tissue, separated from each other by many nonphagocytic cells of fibroblastic type.

The 8 remaining nodules in the group of 10 showed the presence of rather large quantities of injected iron, which, however, could not be identified intracellularly. This iron was observed usually in lacunas between collagen bundles or about the lymphatic and vascular channels. A few lesions showed lining of the collagen fibrils with dense deposits of iron granules, which imparted a bluish tinge to the entire tissue. However, in no case could definite intracellular iron granules be noted except in occasional single perivascular and perilymphatic cells.

QUANTITATIVE STUDY OF LIPIDS

The data on the plasma lipids have already been given. Tissue lipids were studied according to the method described by Montgomery and Osterberg [16] in 3 cases of dermatofibroma and in 7 cases of

16. Montgomery, H., and Osterberg, A. E.: Xanthomatosis: Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch. Dermat. & Syph. **37**:373-402 (March) 1938.

histiocytoma, with rather inconclusive results. As was to be expected, the amount of lipids in the 3 lesions of dermatofibroma was essentially within normal limits; but, surprisingly, this was true also in 2 of the 7 cases of histiocytoma, in 1 of which the nodule histologically was

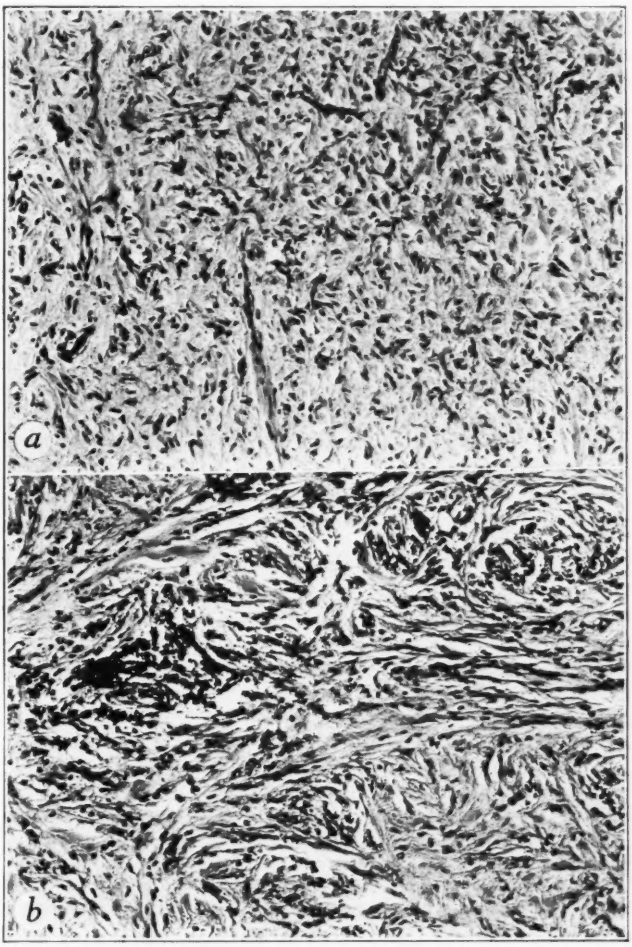

Fig. 5.—(*a*) Dermatofibroma, seventy-two hours after injection of a solution of ferric oxide into the lesion. No phagocytosis of iron is to be seen (Mallory's potassium ferrocyanide stain, × 150). (*b*) Histiocytoma, seventy-two hours after injection of solution of ferric oxide. Intracellular deposits of hemosiderin, photographing black may be noted in localized areas only. Many cells fail to participate in the phagocytosis. Preinjection studies revealed iron and lipids in the phagocytic areas (Mallory's potassium ferrocyanide stain, × 150).

predominantly a foam cell and histiocytic tumor. The highest content of lipids was found in a nodule composed histologically of foam cells, nests and Touton giant cells in a fibrous stroma. This tumor contained cholesterol, 5 mg.; cholesterol esters, 3.7 mg.; lecithin, 2.6 mg.; fatty acids, 8.1 mg., and total lipids, 13.1 mg., per hundred cubic centimeters. The values in this case are comparable to those in nodules of xanthoma tuberosum. In this case the plasma lipids were not determined, but the patient appeared entirely normal on general examination and had no evidence of cardiac disease, diabetes or hypertension.

COMMENT

The clinical findings in our series varied only in minor detail from those in series of cases reported by other authors. We wish to emphasize, however, that the clinical distinction between groups 1 and 2, namely, the distinction between dermatofibroma and histiocytoma, usually is impossible unless phagocytosis has occurred to such a degree as to cause either a xanthic hue, from deposition of lipids, or a bluish color, from deposition of iron.

A history of injury preceding the formation of the nodule was obtained in more than 20 per cent of our cases. This finding, together with the facts that 80 per cent of all lesions occur in the extremities (approximately the same incidence of site as for the particular lesions studied here) and that an injury is frequently of such a minor nature that it passes unnoticed by the patient, we believe lends much support to the view that these nodules constitute a reaction to local disturbance rather than an autonomous new growth or an expression of a systemic pathologic process. We were unable to determine in this series any association between the development of these nodules and the existence of diabetes mellitus or hypertension.

It should be emphasized that in 3 of the 4 cases of multiple lesions studied, lesions belonging both to group 1 and to group 2 were found. On no occasion was malignant change noted in the nodules, nor was total surgical excision followed by recurrence or by the development of keloid. Reports of malignant transformation exist,[17] but, in view of the common occurrence of these nodules as compared with such reports, the incidence of malignant change must be minimal indeed.

17. Gougerot, H., and Dreyfus, B.: Histiocytome malin, ulcéro-végétant; post-traumatique; le traumatisme ayant fait dégénérer un (fibrome) ancien, Bull. Soc. franç. de dermat. et syph. **44**:1699-1703 (July) 1937. Dupont, A.: Histiocytome xanthélasmisé malin de la peau, ibid. **40**:674-677 (May) 1933; Histiocytomes malins de la peau, des gaines tendineuses et des aponévroses, Bull. Assoc. franç. p. l'étude du cancer **28**:456-472 (March) 1939.

In our pathologic study of these lesions, we have divided them into two groups, classification depending on the presence or absence of reticuloendothelial cells. If the groups are to be differentiated, as has been advocated by Woringer, this basis would appear to be the only one on which such a grouping could be attempted. All other changes, such as epidermal thinning, reduction or absence of elastic tissue, dilatation of superficial capillaries of the cutis, atrophy of the dermal appendages and lack of limiting capsules, are common to both.

We noted that only 35 of the 101 lesions revealed clumps of reticuloendothelial cells. Of these 35, the vast majority were composed mainly of fibroblasts and fibrocytes, and histiocytic elements formed relatively small localized collections. The latter invariably revealed lipids, and granules of iron were demonstrated intracellularly in all but 2 lesions. The collections or nests of phagocytes were usually in close proximity to a small vessel, and in 1 lesion evidence of recent gross hemorrhage in the nodule was noted. Hemorrhagic lesions of this type have been described previously.[18] In 2 lesions the inflammatory infiltrate was of such proportion as to suggest a foreign body granuloma.

Thus, in our opinion, lesions of the type of group 2, which corresponds to the histiocytoma of Woringer, should be regarded not as an entity but as a variant of dermatofibroma or of nodular subepidermal fibrosis. We should regard the focal collections of phagocytes as of perivascular origin and as originating in response to hemorrhage, inflammatory changes and local tissue destruction in the nodules.

Whereas nodules of histiocytoma may resemble solitary and, especially, older lesions of xanthoma tuberosum, there is no need, we believe, for grouping histiocytoma with xanthoma, as histiocytoma is not associated with systemic disease. The basis for separation of histiocytoma from xanthoma was outlined by Sendrail and Bazex,[19] who, like Thannhauser,[20] pointed out that massive deposition of lipids is frequently found in lesions of chronic inflammatory nature. Unlike Arnold and Tilden, we failed to find evidence of metabolic disease in a significant proportion of our cases.

Dr. Wolbach loaned us representative slides from the series of cases reported by Gross and Wolbach. Two of our cases of histiocytoma were duplicates of their cases. The lesions in 4 cases of

18. Chatelier, L., and Gadrat, J.: Histiocytome sidérosique, Bull. Soc. franç. de dermat. et syph. **43**:771-777 (April) 1936. Sézary, A.; Horowitz, A., and Lévy-Coblentz, G.: Histiocytome géant hématique, ibid. **44**:1713-1714 (July) 1937.

19. Sendrail, M., and Bazex, A.: Les lipoidoses cutanées, Ann. de dermat. et syph. **1**:166-202, 1941.

20. Thannhauser, S. J.: Lipidoses: Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1940.

dermatofibroma showed considerable vascularization but failed to reveal any histiocytes with intracellular deposits of iron or lipids. In none of the cases in our series could a history of a preceding angiomatous lesion be obtained. Therefore, it is difficult to use the term "sclerosing hemangioma" in our series of cases, in two thirds of which the nodules were composed of connective tissue cells. In Gross and Wolbach's series of cases, sclerosing hemangioma predominated; in Senear and Caro's report, the histologic description in most of the cases fitted that of histiocytoma. It is difficult to reconcile or to explain this variance in the histopathologic picture in the three series of cases. One might conjecture that the degree of vascularity of a nodule of subepidermal fibrosis, which is known to vary greatly, may also vary according to location of the lesion, the nature of the injury sustained and the presence or absence of infection or inflammatory change. A close similarity could be drawn between the extent of new vessel formation exhibited in some cases and the extreme vascularization seen in granuloma pyogenicum, which is known to be a simple reaction to injury and infection.

Of the many synonyms which have accumulated for the lesions under discussion, we much prefer the one advanced by Michelson, namely, "nodular subepidermal fibrosis," as in our opinion these lesions represent not true "new growths" but a hyperplasia occasioned by a local injury or inflammatory process.

SUMMARY AND CONCLUSIONS

A total of 101 lesions, removed from 95 patients, were examined both clinically and histologically. One third of the lesions were shown to contain histiocytic phagocytes; the remaining nodules were entirely fibroblastic.

Clinical distinction between these two groups is impossible unless massive phagocytosis of iron or lipids, or both, has occurred. In cases of phagocytosis, the presence of histiocytes or reticuloendothelial phagocytes may be suspected by the larger size of the lesion and by the blue-black or xanthic hue imparted to it by the phagocytosed material.

Age, sex, race, duration of the lesions and number and location of the lesions are of no importance in differentiation of the two groups. All data obtained on the aforementioned factors coincide closely with those of former authors on this subject.

In more than 20 per cent of all cases, a definite history was obtained of a piercing injury or other trauma or an inflammatory process preceding the development of the lesion. We believe that these factors are of etiologic significance.

The degree of histiocytic tissue present in the nodules exhibiting phagocytosis of lipids and iron granules was observed to be extremely

variable. It is thought that hemorrhage into the nodule and inflammatory cellular destruction may, in most cases, explain the source of lipids and iron in the phagocytic collections.

In 10 cases vital staining for iron was attempted by the method advocated by Senear and Caro. In 8 of these cases no evidence of phagocytosis of iron was noted. The 2 cases in which phagocytic histiocytes were demonstrated had by previous section been shown to contain localized collections of cells laden with iron and lipids.

No increased incidence of diabetes mellitus, hypertension or other metabolic disorder was noted in this series. There was no definite increase in blood plasma lipids, but there was an increase in tissue lipids in the histiocytoma group, the amount differing little from that observed in similar studies of old fibrous nodules of xanthoma tuberosum. We believe, however, that histiocytoma should not be linked with xanthoma, because of the absence of systemic manifestations in histiocytoma. Our observations in this series of cases would lead us to believe that dermatofibroma lenticulare and histiocytoma of Woringer are not separate entities but are parts of the same disease process under differing conditions. Transitions between the two conditions apparently occur. Both conditions may be present at the same time in the same person. The few lesions in our series that agreed with Gross and Wolbach's description of sclerosing hemangioma also seemed to belong to the same disease process, and we are inclined to emphasize the varying vascularity of these nodules as a secondary manifestation following injury and inflammation rather than as a condition of primary etiologic significance. Some evidence is presented that supports a traumatic and inflammatory cause for these lesions, and we would, therefore, recommend that the term nodular subepidermal fibrosis be accepted for the group, but if one wishes to emphasize the type of histologic response, the terms dermatofibroma, histiocytoma and sclerosing hemangioma can still be employed as subheadings.

ADDENDUM

In the three years since Dr. Rentiers completed his thesis, one of us (H. M.) has continued to observe the lesions in a great many new cases of nodular subepidermal fibrosis in which dermatofibroma has predominated over histiocytoma, and only an occasional nodule has revealed enough vascularization to warrant the designation sclerosing hemangioma. Several cases were encountered in which nodules of histiocytoma revealed the presence of lipids but failed to reveal the presence of iron.

Mayo Clinic.

NEW OFFICIAL CLASSIFICATION OF LEPROSY

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NEW YORK

THE FIFTH International Congress for Leprosy was held in Habana, Cuba, from April 3 to April 11, 1948. The Congress was sponsored and organized by the government of Cuba in collaboration with the International Leprosy Association. The previous International Congress of Leprosy had been held in Cairo, Egypt, in 1938. Two hundred and twenty delegates from twenty-six countries attended the Congress.

Much had happened during the previous ten years in the fields of therapeutics, immunology, pathology and epidemiology, and it was not surprising that many interesting reports were made in those fields. But from the standpoint of the dermatologist two features of the Congress are worthy of mention.

One was the agreement on the superiority of the sulfones in the treatment of leprosy. Promin® (sodium p,p'-diaminodiphenylsulfone-N, N'-didextrose sulfonate), diasone® (disodium formaldehyde sulfoxylate diaminodiphenylsulfone), and sulphetrone® (4, 4'-bis[gamma-phenyl-N-propylamino diphenylsulfone-tetra sodium sulfonate]) were, in the opinion of the Congress, the drugs of choice. Since the sulfones were first used by G. H. Faget and his associates at the United States Marine Hospital at Carville, La., this development constitutes a great American contribution to the study of leprosy.

Also of importance to dermatologists, especially to those with teaching responsibility, is the approval of the new classification which will supersede the classification agreed on in Cairo, which had designated cases as lepromatous, neural or mixed. The new classification was originally known as the South American classification, later as the Pan American classification, and will be known now as the classification of Habana.

Dr. V. Pardo-Castello was chairman of the commission on classification and nomenclature, and Dr. H. L. Arnold Jr. and Dr. J. M. M. Fernandez acted as secretaries. Under the guidance of Dr. Pardo-Castello, the following report was drawn by the committee and approved by the plenary sessions.

* Official representative of New York University College of Medicine to the Fifth International Congress for Leprosy.

TEXT OF REPORT

The Classification Committee of this Congress, in a serious attempt to reconcile and unify these apparently discordant systems, arrived at a formula which is believed to be based on a biologic interpretation of the clinical facts. The criteria, on the basis of which the three classes herein defined are established, are in diminishing order of availability: (1) clinical, (2) bacteriological, (3) immunological, and (4) histopathological.

It is proposed that the classification division of leprosy into two types, "polar" (Rabello, 1938) in their essential characteristics and relatively stable in their evolution, be recognized and maintained, and that they be designated:

Lepromatous (malignant, or gravis): symbol, L.

Tuberculoid (benign, or mitis): symbol, T.

It is also proposed that, in addition, recognition be given a *group* of cases of less distinctive or positive characteristics, less stable and less certain with respect to evolution, and that it be designated:

Indeterminate (undifferentiated): symbol, I.

DEFINITIONS

The characteristics of these three classes of leprosy are as follows:

Lepromatous type.—Minimal resistance to the existence, multiplication, and dissemination of the bacilli; constant presence of large numbers of bacilli in the lesions, with a distinctive tendency to form globi; characteristic clinical manifestations in the skin, mucous membranes (especially those of the upper respiratory tract and eye), and/or the peripheral nerves, together with involvement of other organs; regular failure to react to lepromin; pathognomonic granulomatous structure of the lesions; marked stability of type and a tendency to progression. These cases are "infectious" or "open."

Tuberculoid Type.—High resistance to the existence, multiplication, and dissemination of the bacilli; bacteriologically negative as a rule or, if positive, with few bacilli except in reactional states; characteristic clinical manifestations, mainly in the skin and nerves, tending to be limited in extent and varying in degree with the reactivity of the tissue; reactivity to lepromin in a very high percentage of cases; nearly always a tuberculoid granulomatous structure in active lesions; marked stability, and a strong tendency to spontaneous regression in the absence of repeated reactions. These cases are usually "noninfectious" or "closed."

Indeterminate group.—Variable with respect to resistance; clinical manifestations chiefly in the skin and nerves; the skin lesions usually flat macules, either hypochromic, erythemato-hypochromic or erythematous; bacteriologically negative as a rule, or, if positive, with few bacilli; lepromin reaction usually negative or moderately positive; the lesions histologically of simple inflammatory nature; stability much less than in either of the (polar) types; and a variable tendency with regard to persistence, progression, or regression, or transformation into one of the polar types. These cases are usually "noninfectious."

CLINICAL SUBDIVISION OF CASES

The fundamental aim of any classification of a leprosy case being the determination of the type or group to which it belongs, in accordance with the foregoing definitions, certain members of the Classification Committee held that the "sub-

types" of other systems merely correspond to clinical aspects of variable importance. These aspects can be considered from different points of view, namely:

Degree of severity (as, for example, the L_1, L_2, L_3, of the Memorial Conference Classification);

Manner of evolution (slow or rapid, stationary or progressive, reactional states, etc);

Localization (skin, nerve, eye, systemic, etc.);

Morphology (macules, nodules, "plaques," diffuse infiltrations, etc.);

Clinical form (classical nodular lepromatosis, diffuse lepromatosis of Lucio, etc.).

Clinical Notes

CHRONIC URTICARIA DUE TO GIARDIA LAMBLIA

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BROADVIEW, ILL.
and
JAMES H. MITCHELL, M.D.
Clinical Professor Rush Emeritus of Dermatology, University of Illinois; Chairman of the Department of Dermatology, Presbyterian Hospital
CHICAGO

Giardia lamblia, an intestinal flagellate, is generally thought to produce diarrhea in children and occasionally in adults. It has never been cultivated. The spread of the infection is through contamination with fecal material containing the cysts. It inhabits the upper part of the intestinal tract in the trophozoite stage. The fresh unstained stool specimens show numerous cysts and, in this case, an occasional actively motile trophozoite. The trophozoite is said to multiply by longitudinal fission. Detail of the flagellate is visible with iron-hematoxylin preparations. The cysts are ovoid, and in iodine-stained smears nuclei, axostyles and fibrils may be seen.

REPORT OF A CASE

J. S., a boy aged 16, had had attacks of urticaria since the age of 9. He had lived alternately in Florida and Chicago for the past twelve years prior to examination. He had returned to Chicago a year previously. He was first seen in the Central Free Dispensary on Jan. 22, 1947, with an urticarial eruption characterized by wheals up to 1 inch (2.5 cm.) in diameter on the body and especially on the arms, forearms and thighs. A diagnosis of erythema multiforme was made. The patient stated that cold weather seemed to bring on the attacks. A test with ice showed no uritcarial-like response on the normal skin. For the previous five months he had been seen frequently and at all times had had an urticarial eruption.

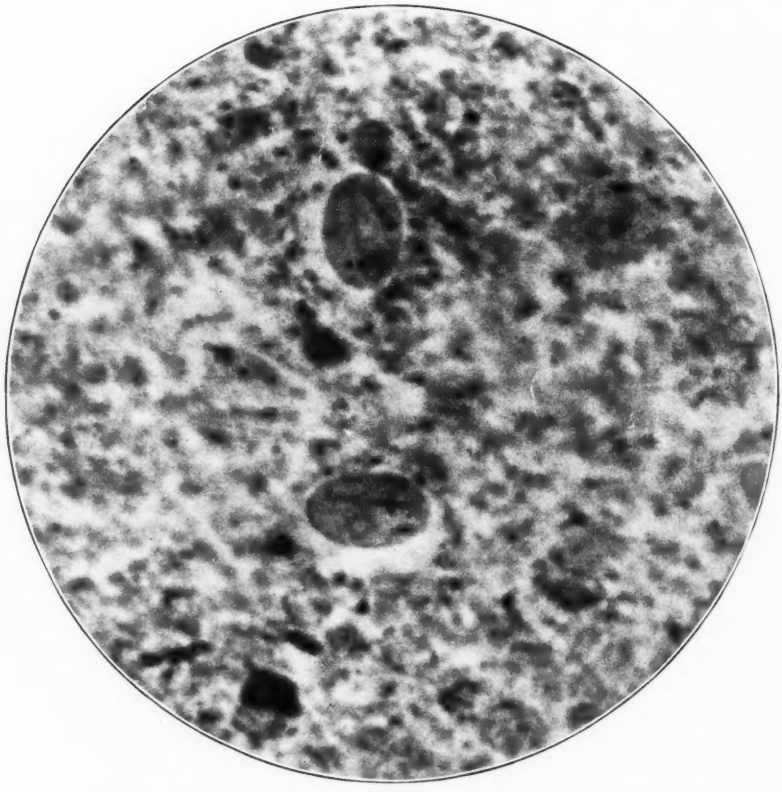
These wheals were evanescent, appearing suddenly and gradually fading. At first, because of a history of taking feen-a-mint® and ex-lax® (phenolphthalein laxative), it was thought that phenolphthalein was the cause, but no phenolphthalein had been taken since he was first seen. He complained of alternating periods of constipation and loose bowel movements and epigastric distress. In February joint pains prompted a suspicion of a streptococcic infection, but no focus of infection was found. He was given sulfathiazole for a week with no improvement. Vitamin C was given over periods of time, and magnesium sulfate salts and magnesium citrate were given for constipation but caused no cessation of the eruption.

Tripelennamine hydrochloride (pyribenzamine hydrochloride®) gave no relief, although it was not given in large doses.

The patient worked in a bowling alley in the evenings as a pin setter and inhalation of the dust was thought to be a causative factor. The day after working he would come to the dispensary with giant urticarial lesions on his thighs, which he experienced after sweating and sitting on the alley rail. He stopped working at this place for several weeks, with no improvement. A diet

which prohibited tea, coffee, chocolate, cocoa and coca cola® had no effect. He was instructed to examine the stool for worms, but none was seen. Because of his recent complaint of loose bowel movements and alternate constipation with mild nausea and epigastric distress, which had occurred frequently before, examination of a stool was made by the bacteriology department, which showed no worms but numerous Giardia lamblia cysts.

Cysts (4 plus) were observed, and several motile Giardia flagellates were seen. Apparently, when motile forms are found, it is assumed that the infec-



Cysts of Giardia lamblia in the fecal smear. The clear zone at the periphery of the cysts can be seen. The longitudinal axostyles, several of the four nuclei and the shield can be seen. The trophozoite is seen rarely in the fecal smear.

tion is severe. He was given quinacrine hydrochloride, 1½ grains (0.098 Gm.), three times a day, and after ten days the urticaria disappeared. His gastric distress also ceased.

Examination of the Blood.—Examination of the blood on January 22 showed hemoglobin 15 Gm., erythrocytes 4,700,000 and leukocytes 8,000. On April 18 the results were: hemoglobin 12.5 Gm., erythrocytes 4,000,000, leukocytes 7,000, neutrophils 53, basophils 1, lymphocytes 44, monocytes 2, eosinophils 0 and

sedimentation rate 9 mm. in 1 hour. On June 6 results were: hemoglobin 13.5 Gm., erythrocytes 4,650,000, leukocytes 8,950, neutrophils 63, basophils 1, lymphocytes 35, monocytes 2 and eosinophils 0.

Urinalysis.—The urine was clear, with a specific gravity of 1.020, acid, albumin 0, sugar 0, mucous shreds, microscopically, and 5 to 8 pus cells.

Examination of the Stool.—On May 16, a smear showed pus cells 0, no blood, Giardia lamblia cysts (4 plus) and Endamoeba coli cysts (1 plus).

Liver serum showed Giardia lamblia (4 plus) and E. coli cysts (1 plus). On medium of Endo Products, Inc., and blood agar, Bacillus coli and Bacillus proteus were seen. Flotation revealed Endo coli cysts (2 plus) and Giardia lamblia cysts (4 plus).

On June 13 (seven days after treatment with quinacrine hydrochloride was started) a smear showed no pus cells, blood, cysts or amebas. Liver serum showed one E. coli cyst. On a medium (Endo Products, Inc.) with blood agar, scant B. coli plus green streptococci were seen. Flotation revealed no ova or cysts.

SUMMARY

A case is presented of chronic urticaria of five months' duration with evidence of Giardia infestation which cleared after administration of quinacrine hydrochloride for a few days. A subsequent examination of the stool showed no evidence of Giardia lamblia. The accompanying symptoms of nausea, epigastric distress and alternate constipation and diarrhea ceased.

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25 East Washington Street (Chicago 2).

MONILIAL INFECTION OF THE THUMB NAIL

Report of a Case

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Candida albicans is known to affect finger nails,[1] producing an onychomycosis, usually accompanied by paronychia. This type of infection is found, most commonly, in persons whose hands are frequently in water. Kingery and Thienes [2] reported an epidemic of monilial paronychia and dermatitis of the hands occurring in the workers of a canning factory where the employees handled fresh fruit. In

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From the Division of Dermatology and Syphilology, Department of Medicine, Duke University School of Medicine, Durham, N. C.

1. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, National Research Council, Division of Medical Science (Military Medical Manual), Philadelphia, W. B. Saunders Company, 1944. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943.

2. Kingery, L. B., and Thienes, C. H.: Mycotic Paronychia and Dermatitis: Hitherto Undescribed Condition Apparently Peculiar to Fruit Canners, Arch. Dermat. & Syph. **11**:186 (Feb.) 1925.

most of the reports in the literature, such as those by Scott,[3] MacCormack[4] and Gray,[5] similar types of predisposing causes were noted.

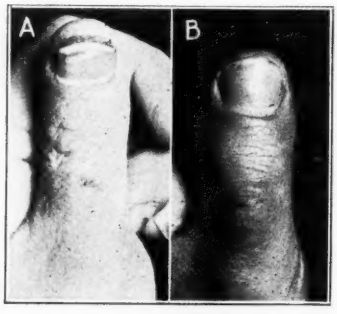
The following case is reported because of the unusual source of infection.

REPORT OF A CASE

J. N., a 4 year old white boy, was seen because of a tender, distorted, crumbling and brown left thumb nail. There was a definite history of thrush of the mouth eighteen months previously, which had been diagnosed by culture and cured by the local use of methylrosaniline chloride U. S. P. (gentian violet). Several weeks later the left thumb became tender, and under the nail there was a pustular exudate. During the subsequent months the nail became brown, distorted, crumbled and somewhat separated from its base (figure, *A*).

The patient had sucked his left thumb since infancy. Despite the efforts of the mother to break this habit during the child's episode of thrush, the thumb sucking had continued.

Examination with a dilute solution of potassium hydroxide and culture of material from the nail revealed C. albicans.



A, left thumb nail before treatment; *B*, left thumb nail after treatment.

The patient was treated by means of potassium permanganate (1:4,000) soaks for his thumb for one-half hour twice daily, followed by application of 1 per cent methylrosaniline chloride in a 10 per cent solution of alcohol to the thumb and finger. Sodium propionate ointment was applied to the thumb twice daily after it had been painted with methylrosaniline chloride. The finger slowly improved, and at the end of a four month period the nail was entirely normal (figure, *B*).

SUMMARY

The case of a 4 year old child who had an infection of the left thumb nail with C. albicans is reported. The case is interesting because of the unusual source of infection. The child was a thumb sucker and had acquired his infection while he had a monilial infection of the mouth.

18 Montague Street.

3. Scott, J. A.: Oidiomycosis of the Nails, Brit. J. Dermat. **39**:119, 1927.

4. MacCormack, H.: Paronychia Due to Oospora (Oidium) Albicans, Brit. J. Dermat. **39**:394, 1927.

5. Gray, A. M. H.: Paronychia Due to Yeast-Like Organism with Curious Discoloration of the Nails, Proc. Roy. Soc. Med. **24**:397, 1931.

RINGWORM OF THE SCALP

HAROLD SHELLOW, M.D.
CHICAGO

In ringworm infection of the scalp (tinea capitis) in children, both from the standpoint of esthetic appearance and as a preventive means against contamination of others by direct or indirect contact, the time-honored wearing of skullcaps has been very effective. Most popularly, the skullcap is made at home, the upper part (the reenforced top) of a woman's stocking being used.

Women's nylon hose are again constructed entirely of nylon, and it has been noted that when skullcaps made from such material are worn by children with tinea-infected hair, they afford but little protection to other children who are exposed to the infection. It seems that the character of the nylon thread produces a meshed material that permits easy protrusion of hairs from the scalp. This is especially so when the hair is close cropped. In active cases of ringworm of the scalp examination under the Wood light when such skullcaps are worn and in place reveals fluorescent hairs protruding. They do not do so when caps are made of cotton or rayon stockings, as they were in the past, or of other closely woven materials.

The incidence of ringworm of the scalp in children does not seem to be abating, which fact may be due in part to improper shielding of the scalp with ineffective skullcaps, such as those made from nylon hose. It is therefore suggested that parents be warned of the ineffectiveness of skullcaps made from the present all-nylon stockings and that some other material, such as cotton or rayon or linen, be used. In this way either direct or indirect contamination could be minimized.

116 South Michigan Avenue.

News and Comment

GENERAL NEWS

Specialists Certified by the American Board of Dermatology and Syphilology, Inc.—At the meeting of the American Board of Dermatology and Syphilology held in New York, April 1 to 3, 1949, the following candidates were certified:

Michael Bolus, Raleigh, N. C.; Adrian Brodey, New York; Rachel Burstein, New York; Paul C. Campbell Jr., Washington, D. C.; John F. Daly, Bellmore, N. Y.; Calvin C. Ellis, University City, Mo.; Helen Fabian, New York; Joseph A. J. Farrington, Jacksonville, Fla.; Harry L. Feigenbaum, Brooklyn; Thomas E. Gibson, Bakersfield, Calif.; Herman Glassman, Miami, Fla.; Natalie D. Goldberg, Brooklyn; James H. Gosman, Indianapolis; Antony J. Greco, Santa Monica, Calif.; Hubert L. Harris, Brookline, Mass.; Samuel D. Kaplan, Elizabeth, N. J.; Marvin D. Knoll, Van Nuys, Calif.; Alwyn T. Kornblee, Tulsa, Okla.; Edward L. Laden, Chicago; Howard F. Lawrence, New York; Louis S. Leland, Washington, D. C.; Lawrence B. McCaleb, Washington, D. C.; Frank M. Melton, Durham, N. C.; Richard M. Oliver, Chicago; Clement B. Potelunas, Wilkes-Barre, Pa.; Herman H. Rodin, South Bend, Ind.; Harvey C. Roll, Evanston, Ill.; Julius L. Rosenfeld, New York; Seymour Shapiro, Hollywood, Calif.; Joseph H. Shepard, Columbus, O.; Jacob Slone, Pittsburgh; Conrad Stritzler, Jamaica, N. Y.; Frederick J. Szymanski, Chicago; Jules Eli Vandow, New York, and Alfred L. Weiner, Cincinnati.

The following candidates also took the examination, but are not considered certified specialists of the Board until they have completed five years in the specialty:

Harvey B. Ansell, New York; Charles D. Bell, St. Albans, N. Y.; Arthur Bobroff, Bronx, N. Y.; Harry M. Brown, Los Angeles; Irving D. Ehrenfeld, Bronx, N. Y.; Mortimer S. Falk, Philadelphia; Henry D. Garrett, El Paso, Texas; Daniel B. Glickman, Brooklyn; David S. Gudes, Detroit; Robert H. Harris, Broadview, Ill.; Robert D. Hubbard, Utica, N. Y.; G. W. James, Winston-Salem, N. C.; Edgar B. Johnwick, Washington, D. C.; Norman B. Kanof, New York; Henry M. Lewis, Denver; Wilbur B. Light, Lima, Ohio; Irving D. London, Montgomery, Ala.; William G. McCreight, Rochester, Minn.; William E. McDaniel, Cincinnati; Walter B. Shelley, Chester, Pa.; Milton B. Sloane, Englewood, N. J.; Albert A. Soifer, Flushing, N. Y.; Malcolm C. Spencer, Philadelphia; Robert C. Thompson, Charlottesville, Va.; Bette Young Upshaw, Rochester, Minn.; Karl Violin, New York, and Marcus A. Weiner, Washington, D. C.

American Academy of Dermatology and Syphilology.—The annual meeting of the American Academy of Dermatology and Syphilology will be held at the Palmer House, Chicago from Dec. 5 to 8, inclusive, 1949. Applications for space in the Scientific Exhibit should be sent to Dr. Samuel M. Bluefarb, 30 North Michigan Avenue, Chicago.

Society for Investigative Dermatology.—The Tenth Annual Meeting of the Society for Investigative Dermatology will be held at the Ritz-Carlton Hotel, Atlantic City, N. J., on Saturday and Sunday, June 11 and 12, 1949. After the afternoon session on Saturday, June 11, a dinner will be held for members and guests.

Book Reviews

Racial Variations in Immunity to Syphilis: A Study of the Disease in the Chinese, and Negro Races. By Chester North Frazier and Li Hung-Chiung. Price, $2.50. Pp. 122. Chicago: The University of Chicago Press, 1948.

The authors have presented an analytic comparison of three syphilitic groups, the white and Negro races of Baltimore, Md., and the Chinese race of Peiping, China. Their study led them to conclude that, regardless of sex or race, the disease is essentially the same in all people. Syphilis was found to be a less serious disease in the Chinese than in either white or Negro races. This is demonstrated by the frequency of latency. The proportion of latency in the Chinese male approached that in the white female.

Early in the disease, the Chinese were found to react more violently than the white or Negro races. Chinese males were fifteen times as often the subjects of skeletal lesions and twice as often the subjects of symptomatic meningeal lesions as white males. However, as the infection progressed into the later stages, the excess of neural localization in the Chinese male was not sustained.

In the white race it was the neural structure which bore the weight of the disease, while in the Negro the cardiovascular system was more often involved. When lesions of the cardiovascular and the nervous system were taken together, the white race exhibited more serious pathologic changes than the Negro and the Negro more serious involvement than the Chinese.

Syphilis is milder in the female than in the male, as is seen by the preponderance of latency and the frequency of benign localization in the tertiary stage. The male type of the disease is vascular and neural and the female type is cutaneous, with a greater tendency to latency. The disease in the Chinese people was found to be more of the female type. This was seen in the early activity of the cutaneous and skeletal systems, the frequency of latency and in the relative infrequency of cardiovascular disease and neurosyphilis.

The Chinese dietary habits are unique. If nutritional factors affect host resistance to Treponema pallidum or determine localization of the disease, the only evidence of this was found in the unusual susceptibility of the Chinese to the skeletal involvement. The authors conclude that since the Chinese, whether male or female, approached the milder pattern of female reaction to syphilis it is reasonable to assume that some inherent factor is responsible for this difference. In the Chinese there are certain qualities of bodily form and mental aptitude which indicate a strong feminine component of the bisexual fusion of this race.

Handbook of Diseases of the Skin. By Richard L. Sutton, M.D., and Richard L. Sutton Jr., M.D. Price, $12.50. Pp. 749, with 1,057 illustrations. St. Louis: The C. V. Mosby Company, 1949.

This new volume by the Suttons carries on a well established family tradition of dermatologic textbook writing. It is intermediate in size between the "Synopsis" and the "Introduction to Dermatology" by the same authors. Literally, it is a handbook, both by title and by virtue of the tremendous wealth of material the authors have packed between the covers of this conveniently sized book.

It is well bound and is replete with 1,057 illustrations. There are hundreds of clinical photographs, and the authors have attempted to include at least one picture

of each entity. Unfortunately, however, many of the photographs are too small to portray detail accurately and accordingly are of little value. The authors would have done better to have used larger, illustrative pictures instead of the many vague small ones. This same comment also applies to some of the histopathologic photomicrographs.

The book is heavily documented, the bibliographic references numbering several thousand, and these, having been abbreviated to a minimum, are incorporated within the textual material. Almost all declarative statements are documented, so that one can find immediately sources of ideas and opinions which have been mentioned briefly in the text. At times, however, this ponderous documentation gives the subject matter the appearance of a review article in a current journal rather than a passage in a textbook. This feature might prove disadvantageous to the undergraduate student of dermatology, who needs a concise, orderly exposition of disease process to use as a guide rather than a multiopinionated, self critical, theoretic discussion.

The authors are to be complimented on their attempt to use a true nosologic classification of subjects in the table of contents rather than the time-worn pathologic divisions.

The book is printed in two sizes of type, the larger being used for essential material for basic undergraduate study and the smaller for more detailed and specialized information.

In the section on syphilis, which covers 61 pages, the authors have at least mentioned almost every clinical manifestation of the disease. Unfortunately, a considerable portion of this section is printed in such small type that it is virtually readable for only a few minutes at a time. Perhaps a less complete but more readable discourse might have been preferable.

Many sections of the book are notably well done, such as the discussion of contact dermatitis, which includes a comprehensive survey of methods of identifying contact irritants; the chapter on dermatoses due to metabolic disturbances, and the presentation, in outline form, of cutaneous manifestations due to vitamin deficiency.

This volume provides a fund of readily available source material for all interested in the specialty of dermatology.

Atlas of Oral and Facial Lesions and Color Film Library. By Ralph Howard Brodsky. Price $80. Pp. 127, with 100 colored slides. Baltimore: The Williams & Wilkins Company, 1948.

This is a primer of facial and oral lesions which presents a great variety of material in a superficial, brief manner. The continuity of the text does not seem as well organized as it might be.

The author stresses the use of "grenz irradiation" and "pan-vitamin therapy" for such conditions as geographic tongue and leukoplakia. Oral galvanism is also emphasized as a cause of burning tongue and is considered etiologic in aphthous stomatitis, certain types of gastrointestinal distress and possibly certain types of headaches.

On a basis of value received, the cost of the book and the library of slides seems prohibitive. The excellence of 100 slides can hardly be judged from the 3 sample slides sent for review. Conceivably, the library of slides might have an elementary teaching value for those who have had neither the experience nor the material necessary to gather a personal collection of photographs and slides.